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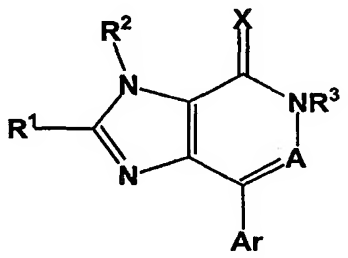

(I)

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I), and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart–related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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TITLE

1H-Imidazo[4,5-d]pyridazin-7-ones, 3H-Imidazo-[4,5-c]pyridin-4-ones and Corresponding Thiones as Corticotropin releasing Factor (CRF) Receptor Ligands

FIELD OF THE INVENTION

This invention relates a treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress, by administration of certain 1H-imidazo[4,5-d]pyridazin-7-ones, 3H-imidazo-[4,5-c]pyridin-4-ones and corresponding thiones.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog.*

Horm. Res. 39:245 (1983); G.F. Koob, *Persp. Behav. Med.* 2:39 (1985); E.B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimerís disease, Parkinsonís disease, Huntingtonís disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional

support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces ìanxiolytic-likeî effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the ìanxiogenicî effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142)

enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α-helical CRF_{9-41}) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces ìanxiolytic-likeî effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Several publications describe corticotropin releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050 , Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder,

fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal

interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in a mammal.

The present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a mammal.

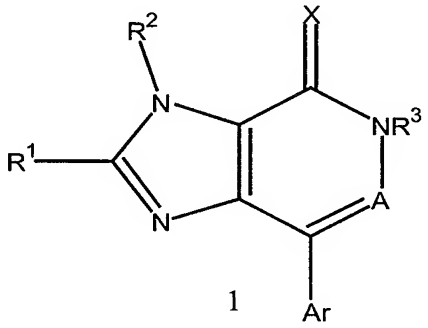
According to another aspect, the present invention provides novel compounds of Formula (1) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of Formula (1) and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the invention, the compounds provided by this invention (and especially

labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

DETAILED DESCRIPTION OF INVENTION

[1] The present invention comprises novel compounds of Formula (1) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. This invention comprises compounds of Formula (1):



and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

X is O or S;

A = N or CR^9;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-

benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached via an unsaturated carbon atom;

R^1 is independently selected at each occurrence from H, C_1-C_4†alkyl, C_2-C_4†alkenyl, C_2-C_4†alkynyl, halo, CN, C_1-C_4†haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from:
-H, aryl, heteroaryl and heterocyclyl,
or
-C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^3 is selected from:
-H, aryl, heteroaryl and heterocyclyl,
or
C_1-C_4†lkyl, C_3-C_6†alkenyl, C_3-C_6†alkynyl, C_3-C_6†cycloalkyl, C_4-C_{10} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl,

cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12}†cycloalkylalkyl, NO_2, halo, CN, C_1-C_4†haloalkyl, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12}†cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7 are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†aloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl optionally substituted by halogen, C_1-C_4 alkoxy or C_1-C_4 halo-alkoxy (1 to 4 halogens);

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$,

COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

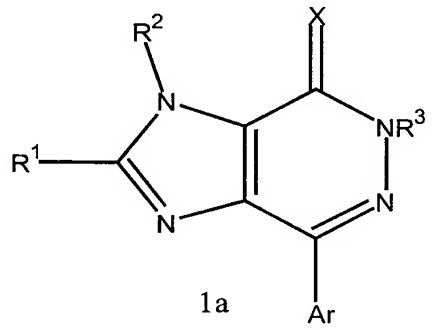
heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2.

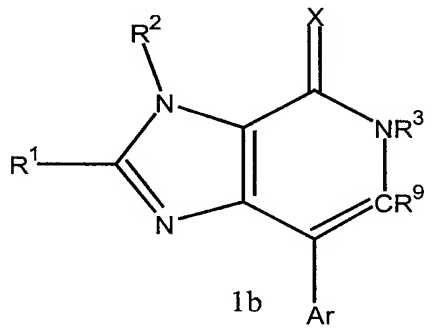
[2] Preferred compounds of the above invention also include compounds of Formula (1) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl or pyridyl, each optionally substituted with 1 to 4 R^4 substituents.

[3] More preferred compounds of the above invention also include compounds and isomers thereof of formula 1 wherein A is equal to nitrogen (formula 1a), stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.



1a

[4] The present invention also relates to compounds, compositions, and stereoisomeric forms, pharmaceutical salts or pro-drugs thereof wherein, in a compound of formula 1, A is equal to CR^9 (formula 1b):



1b

[5] More preferred compounds of the invention include those compounds of formula 1 wherein X is equal to oxygen.

[6] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof

wherein Ar is phenyl or pyridyl and each Ar is optionally substituted with 1 to 3 R^4 substituents.

[7] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^2 is:

- C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl.

[8] More preferred compounds also include those compounds of formula 1 wherein R^1, R^2 and R^3 are independently selected at each position from zC_{1-6} alkyl.

[9] The present invention comprises a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections,

hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formula (1) with the variables as recited above.

The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with the variables as recited above and a pharmaceutically acceptable carrier.

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight

chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(*S*)" means the S enantiomer and the prefix "(*R*)" means the R enantiomer. Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a

stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

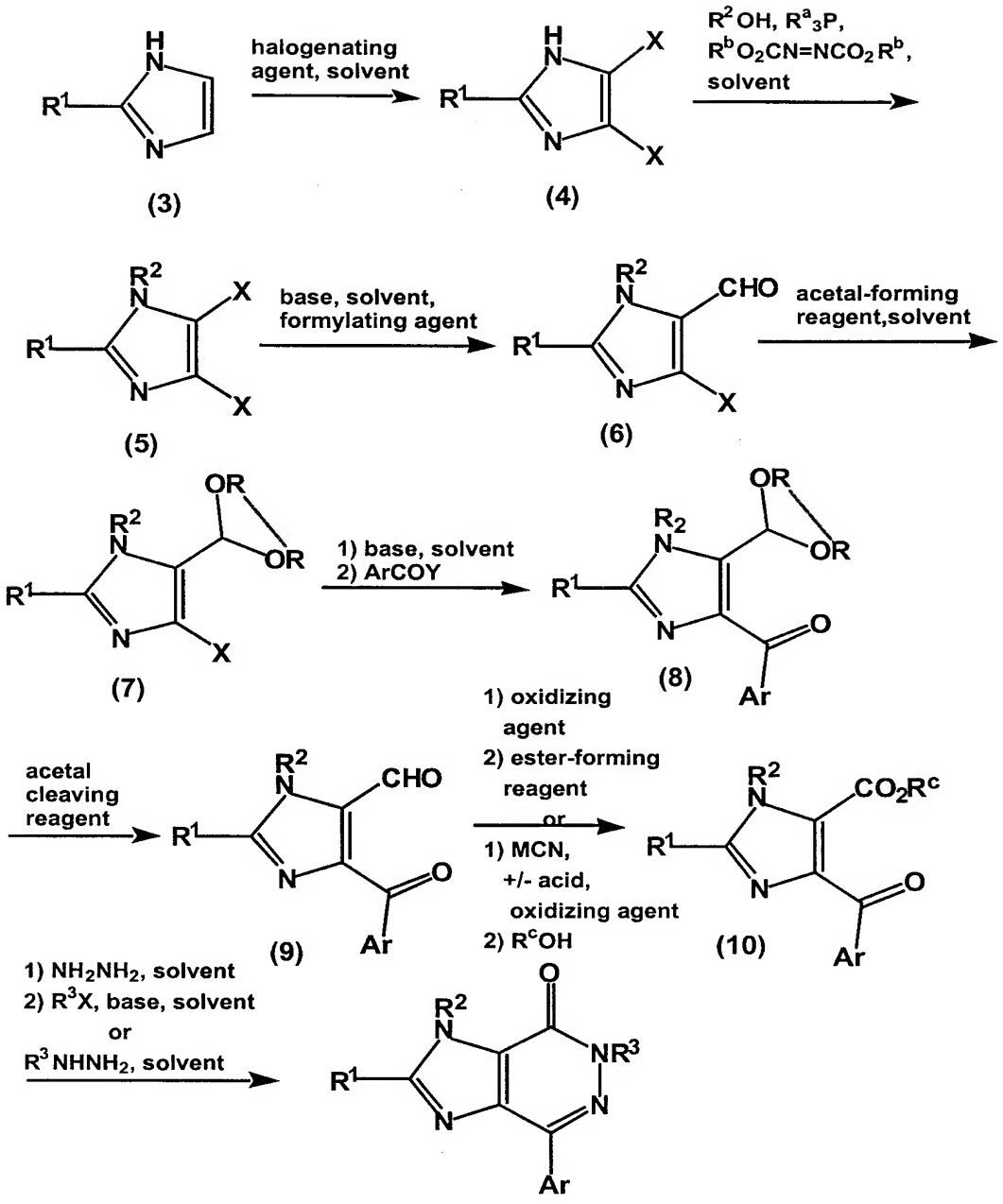
Syntheses

Some compounds of Formula (1) where X = O and A = N, may be prepared from intermediate compounds of Formula (3) using the procedures outlined in Scheme 1. Compounds of Formula (3) may be treated with a halogenating agent in the

presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (4) (where X is halogen). Halogenating agents include, but are not limited to, Br_2, Cl_2, I_2, N-bromosuccinimide, N-iodosuccinimide or N-chlorosuccinimide. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 150°C. The resulting intermediates (4) may then be reacted with alcohols R^2OH, where R^2 is defined above, in the presence of phosphines $R^a{}_3P$ (where R^a is lower alkyl, phenyl or substituted phenyl or furyl) and an azodicarboxylate ester $R^bO_2CN{=}NCO_2R^b$ (where R^b is lower alkyl) in an inert solvent at temperatures ranging from -80°C to 150°C. Inert solvents may include, but are not limited to, polyethers (preferably 1,2-dimethoxyethane), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane) or aromatic hydrocarbons (preferably benzene or toluene). The choices of phosphine, solvent or azodicarboxylate ester are known to those skilled in the art as described by O. Mitsunobu (Synthesis, 1 [1981]). Intermediates (5) are treated with a base or an alkali metal in an inert solvent and then reacted with formylating agents

YCHO. Y is a halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano group. Bases may include, but are not limited to, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkaline earth metal halides (e.g. methylmagnesium bromide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide) and alkali metal bis(trialkylsilyl)-amides (preferably sodium bis(trimethylsilyl)amide). Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Scheme 1



(1) where A = N, X = O

The resulting aldehydes (6) may be converted to acetals (7) by treatment with an acetal-forming reagent in the presence or absence of an acid in an inert solvent. The dotted line between the R groups means that they may or may

not be connected. Acetal-forming reagents may be alcohols ROH, where R is lower alkyl, diols HOR---ROH where R---R is lower alkylene, or orthoesters $HC(OR)_3$ where R is lower alkyl. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C.

Acetals (7) may then be reacted with a base in an inert solvent, followed by treatment with a compound ArCOY (where Y is a halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano group) to afford intermediates (8). Bases may include, but are not limited to, alkyl lithiums, alkali metal dialkylamides (preferably lithium di-isopropylamide) or alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane or aromatic hydrocarbons (preferably benzene or toluene). Intermediates (8) may then be converted to

compounds of Formula (9) by treatment with an acetal-cleaving reagent in an inert solvent. Acetal-cleaving reagents may include, but are not limited to, hydrochloric acid, sulfuric acid, phosphoric acid, alkanoic acids, alkylsulfonic acids, substituted phenylsulfonic acids, camphorsulfonic acid or haloalkylsulfonic acids. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene).

The keto-aldehydes (9) may be converted to esters (10) by treatment with an oxidizing agent in an inert solvent to give a carboxylic acid, followed by treatment with an ester-forming reagent. Oxidizing agents include transition metal oxides, such as CrO_3 or $KMnO_4$ (with or without a buffering agent such as NaH_2PO_4), pyridinium dichromate or pyridine-SO_3 complex. Inert solvents include water, alkanones (e.g. acetone), aqueous solutions of HCl or H_2SO_4, or N,N-dialkylformamides. Ester-forming reagents include but are not limited to alcohols R^COH, where R^C is lower alkyl, or orthoesters $HC(OR^C)_3$ or combinations of a halogenating reagent and an alcohol R^COH used sequentially or in the same reaction. Halogenating agents include, but are not limited to, $POCl_3$, $(COCl)_2$, $SOCl_2$, N-halosuccinimides, PCl_3, PCl_5 or PBr3. Inert solvents for the halogenation include, but are not limited to, aromatic hydrocarbons (preferably benzene or toluene), aromatic amines (e.g. pyridine) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably

dichloromethane). Preferred reaction temperatures range from 0°C to 150°C.

Alternatively, aldehydes (9) may be reacted with a compound MCN, where M is H, alkali metal or tetraalkylammonium moiety, in an inert solvent, treated with an oxidizing agent and reacted with alcohols R^cOH where R^c is lower alkyl. Oxidizing include, but are not limited to, transition metal oxides, such as CrO_3 or MnO_2, pyridine-chromium complexes, such as $CrO_3.C_5H_5N$, pyridinium dichromate or pyridinium chlorochromate or an oxalylchloride-dimethylsulfoxide-triethylamine reagent system, commonly called the Swern oxidation system (D. Swern et al., J. Organic. Chem., 43, 2480-2482 (1978)). Inert solvents of the oxidation include, but are not limited to, halocarbons of 1 to 6 carbons, preferably dichloromethane or 1,2-dichloroethane, lower alkyl alcohols, preferably ethanol or methanol, or lower alkanoic acids, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or combinations thereof.

Esters (10) may then be converted to compounds of Formula (1) where X = O and A = N by one of two methods. Esters (10) may be reacted with hydrazine or its hydrate in an inert solvent, then treated with an alkylating agent in the presence or absence of a base in an inert solvent to provide compounds of Formula (1) where X is O and A = N. Phase transfer catalysts (e.g. tetra-alkylammonium halides or hydroxides) may be optionally employed for the alkylations.Alternatively, esters (10) may be reacted with compounds of Formula R^3NHNH_2 (where R^3 is defined above) in the presence or absence of a base in an inert solvent. Alkylating agents are compounds of the formula R^3Z, where Z is halogen, alkanesulfonyloxy (e.g. mesylate), substituted phenylsulfonyloxy (e.g. tosylate) or haloalkanesulfonyloxy (e.g. triflate) groups. Bases may include, but are not limited to, alkali metal carbonates, alkali metal

bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, water, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene), haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane) or combinations thereof. Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (1) where A = N and X = O may be converted to compounds of Formula (1) where A = N and X = S according to the procedures outlined in Scheme 2. Compounds of Formula (1) where A = N, X = O and R^3 = H may be converted to compounds of Formula (1) where A = N, X = S and R^3 = H by treatment with a thiocarbonyl-forming reagent in an inert solvent. Thiocarbonyl-forming reagents include but are not limited to, P_2S_5 or Lawessonís reagent. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic

amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 160°C. These intermediates may then be converted to compounds of Formula (1) where A = N, X = S and R^3 is not equal to H by treatment with an alkylating agent in the presence or absence of a base in an inert solvent. Alkylating agents are compounds of the formula R^3Z, where Z is halogen, alkanesulfonyloxy (e.g. mesylate), substituted phenylsulfonyloxy (e.g. tosylate) or haloalkanesulfonyloxy (e.g. triflate) groups. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 150°C. Alternatively, Compounds of Formula (1) where A = N, X = O

and R^3 is not equal to H may be converted to compounds of Formula (1) where A = N, X = S and R^3 is not equal to H by treatment with a thiocarbonyl-forming reagent in an inert solvent. The reagent and inert solvent are defined above.

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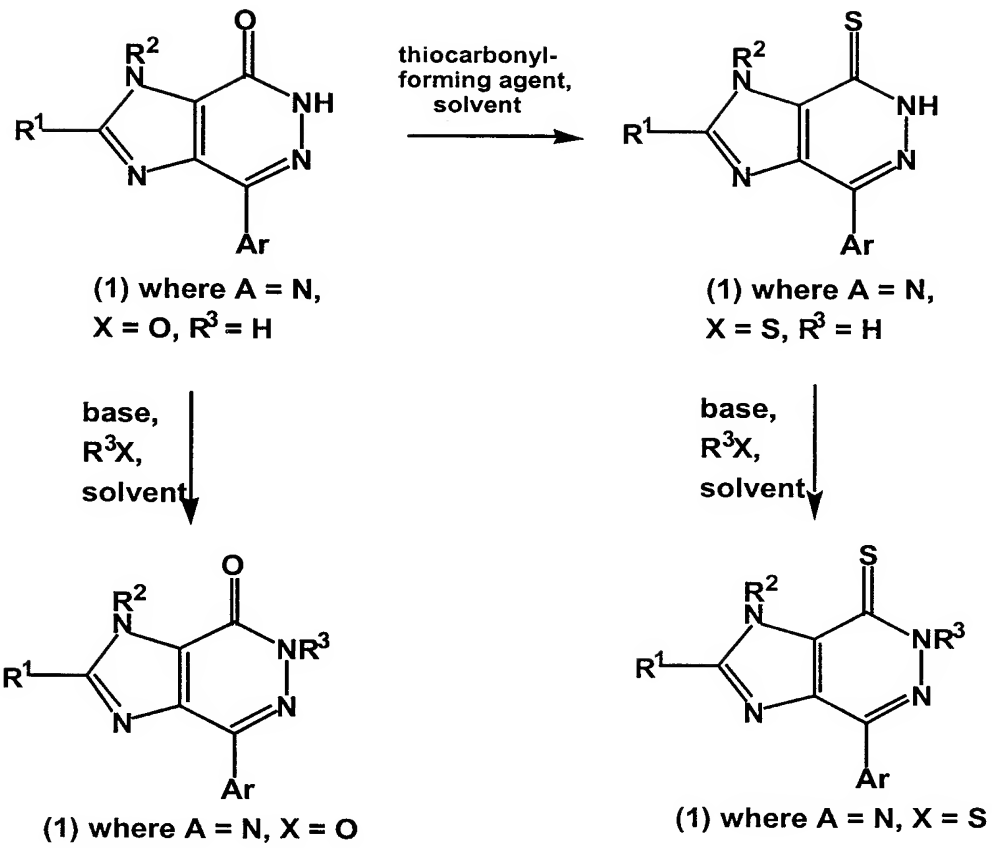
Scheme 2

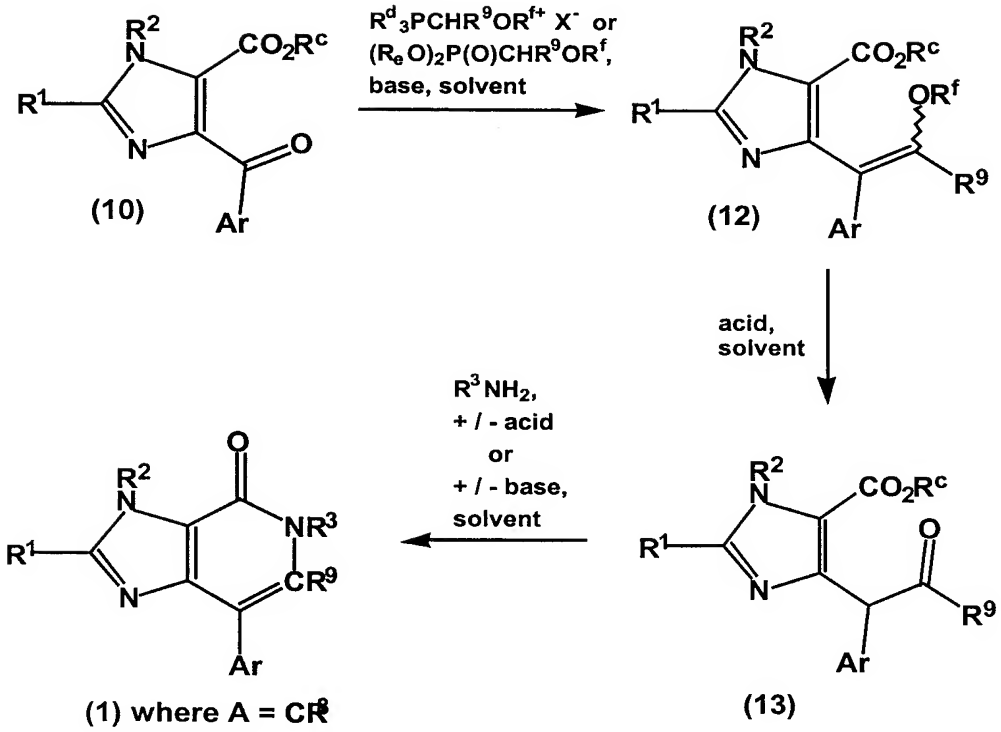


Compounds of Formula (1) where A = CR^9 may be prepared from esters (10) by the methods outlined in Scheme 3. Esters (10) may be treated with phosphonium salts of the formula $R^d{}_3PCH\ R^9OR^{f+}\ X^-$ where R^d is phenyl or substituted phenyl or phosphonates $(R^eO)_2P(O)CHR^9OR^f$ in the presence of a base in an inert solvent to give enol ethers (12). Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium

bis(trimethylsilyl)amide). Inert solvents include, but are not limited to, dialkyl ethers (preferably diethyl ether) or cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane). Intermediates (12) may be hydrolyzed to give intermediates (13) in the presence of an acid in an inert solvent. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C. Aldehydes (13) may be treated with amines R^3NH_2 to generate compounds of Formula (1) where A = CR^8 in the presence or absence of an acid or base in an inert solvent. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to

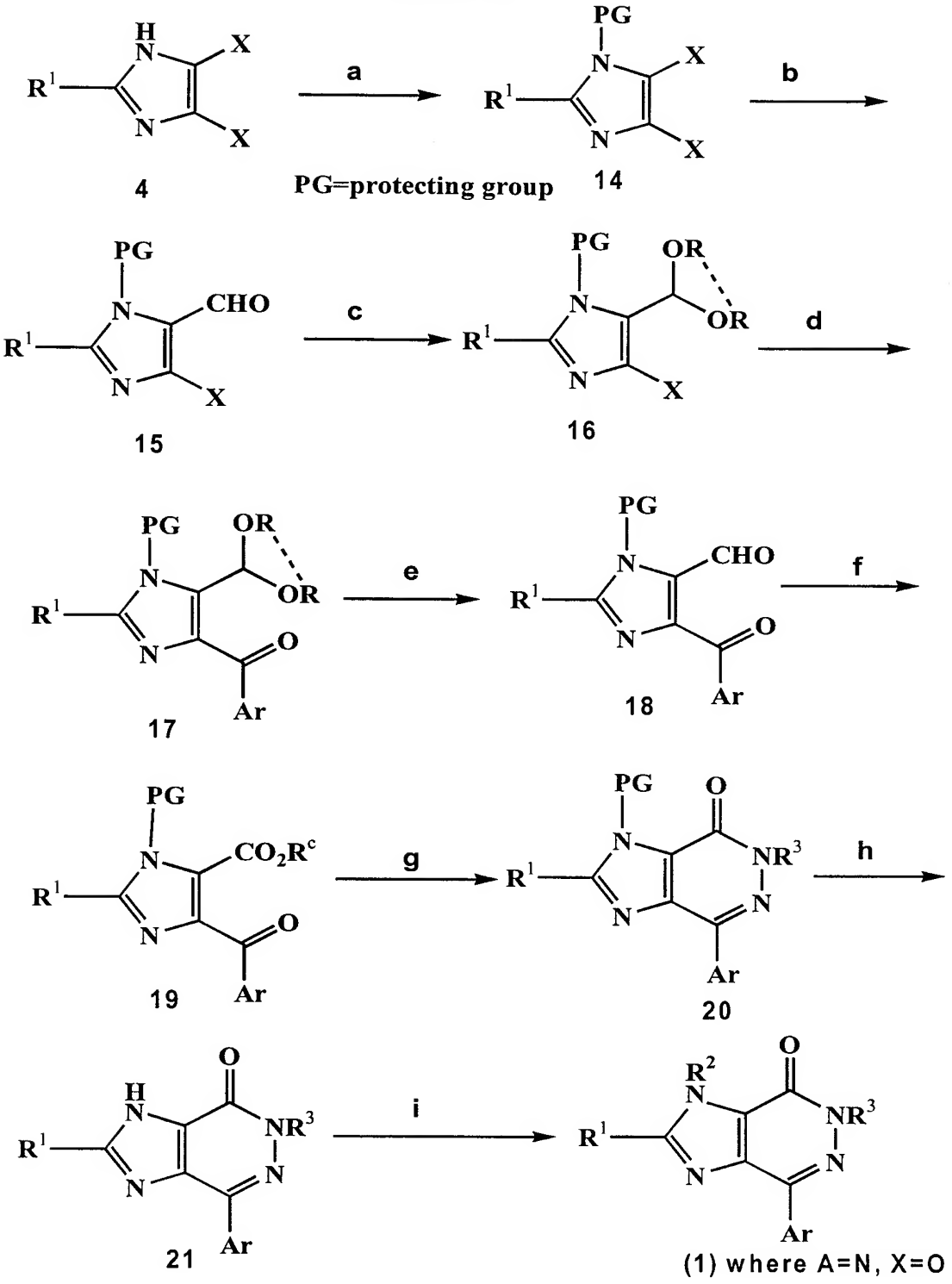
6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred temperatures range from ambient temperature to 150°C.

Scheme 3


R2
CO2Rc
R1
N
O
Ar
(10)
Rd3PCHR9ORf+ X- or
(ReO)2P(O)CHR9ORf,
base, solvent
ORf
R9
(12)
acid,
solvent
R3NH2,
+ / - acid
or
+ / - base,
solvent
NR3
CR9
(1) where A = CR8
(13)

5

Scheme 4


a
b
c
d
e
f
g
h
i
PG=protecting group
4
14
15
16
17
18
19
20
21
(1) where A=N, X=O

Reagents: (a) PG-X / base / solvent, (b) base, solvent, formylating agent, (c) acetal-forming reagent, (d) base, solvent, ArCOY, (e) acetal cleaving reagent, (f) 1. oxidizing agent, 2. ester-forming reagent or MCN, +/- acid, R^cOH, (g) 1. NH_2NH_2, solvent, 2. R_3X, base, solvent or R_3NHNH_2, solvent, (h) deprotecting agents, (i) mitsunobu reactio or R_2X, base, solvent

Alternatively, imidazo[4,5-d]pyridazin-7-ones may be obtained from intermediate (4) as shown in Scheme 4. The intermediate (4) may converted to compound of formula (14) using protecting groups but not limited to benzyl, p-MeO-benzyl or benzyloxymethyl groups. Compound 14 may be converted to compound 20 using the conditions previously described for Scheme 1. Compound 10 may then be deprotected to its NH derivative (21) by standard conditions known in literature. Compound 21 may alkylated under mitsunobu conditions described in Scheme 1 or by alkylation using a base and alkyl halides in the presence of a solvent.

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on an Varian FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the

general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography (thin layer (TLC) or preparative) was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Example 1 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

Part A: 4,5-dibromo-2-ethyl-1H-imidazole
Method A:
A solution of 2-ethylimidazole (57.6 g, 0.6 moles) in $CHCl_3$ (700 mL) was cooled to 0- 5 °C and then bromine was added (76.8 mL, 1.5 moles) dropwise over 60 min under nitrogen atmosphere. The mixture was stirred at 5 °C for 60 mins and then at room temperature for 2 days. TLC (1:10 MeOH / CH_2Cl_2) revealed disappearence of starting material (Rf=0.25) and showed a new spot (Rf=0.45). The mixture was cooled back to 0 °C and a 2N aq. NaOH solution (750 mL) added dropwise to dissolve the yellow solid separated from the mixture. The aqueous layer was separated and extracted the organic layer with 250 mL of 2N NaOH. The combined aqueous extracts was acidified to pH 8.0 using a concentrated HCl solution. The cream-colored solid separated and it was filtered, washed with water and dried in vacuo at 50 °C to afford 55.0 g of desired

product (mp 149-150 °C, 36 % yield): ^{1}H NMR ($CDCl_3$): δ 1.27-1.3 (t, 3H, CH_3), 2.7-2.8 (q, 2H, CH_2). Mass spectrum (CI-NH_3) *m/z*: 255.0 (M+H).

Method B :
To a solution of imidazole (2.32 g, 0.0242 moles) in DMF (30.0 mL) was added $KHCO_3$ (6.1 g, 0.061 moles) and then added bromine (3.12 mL, 0.061 moles) dropwise over 30 mins. at room temp. The mixture was then stirred at 70 °C for 4 hours and then cooled to room temp. TLC (1:10 MeOH/ CH_2Cl_2) revealed a new spot (Rf=0.45) along with disappearence of starting material (Rf=0.25). The inorganic materials were filtered, washed the inorganic solids with ethyl acetate and concentrated the filtrate in vacuo to an oil. The oil was treated with water (50.0 mL) and the resulting solid was filtered and dried to afford 4.59 g of a solid ((mp, 149-150 °C, 75 % yield).

Part B: 4,5-dibromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole:
A mixture of part A material (8.3 g, 0.033 moles), triphenylphosphine (9.4 g, 0.036 moles) and molecular sieves (10 g) in THF (100 mL) was cooled to 0 to -5°C and then 3-pentanol (3.4 g, 0.039 moles) was added under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 mins and then diisopropylazodicarboxylate (7.2 g, 0.033 moles) was added dropwise over 20 min. The mixture was stirred at 0 °C for 2 hours followed by room temperature for 2 days and TLC (1:50 MeOH / CH_2Cl_2) revealed a new spot at Rf=0.5. The reaction mixture was filtered, the collected solid was washed with dichloromethane and the solvent was removed in vacuo to afford yellow liquid. The crude was purified by flash column chromatography using chloroform as

eluent to afford 4.9 g (46.5 %) of colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.79-0.84 (t, 6H, 2*CH_3), 1.3-1.35 (t, 3H, CH_3), 1.82-2.18 (m, 4H, 2*CH_2), 2.65-2.72 (q, 2H, CH_2), 3.95 (m, 1H, CH). Mass spectrum (CI-NH_3): *m/z* 325.0 (M+H).

Part C: 4-bromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde:

A solution of Part B material (3.7 g, 0.0114 moles) in THF (40.0 mL) was cooled to - 78 °C under nitrogen atmosphere and then a 1.6 M n-BuLi solution in hexane (7.4 mL, 0.0119 moles) added dropwise over 30 mins. The mixture was stirred at -78 °C for 1h and then DMF (2.7 mL, 0.0342 moles) was added dropwise over 15 min. The mixture was stirred at -78 °C for 60 min and quenched with saturated NH_4Cl (10 mL) at -78 °C. TLC (1:50 MeOH / CH_2Cl_2) revealed a new spot at Rf=0.55 along with disappearence of starting material spot at Rf=0.5. The reaction mixture was extracted with diethyl ether (3 * 25 mL), washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to afford a yellow oil which was purified by flash column chromatography on silica gel using chloroform as eluent to afford 1.97 g (64 % yield) of colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.73-0.83 (t, 6H, 2*CH_3), 1.35-1.40 (t, 3H, CH_3), 1.59-2.17 (m, 4H, 2*CH_2), 2.72-2.80 (q, 2H, CH_2), 3.95 (m, 1H, CH), 9.67 (s, 1H, CHO). Mass spectrum (CI-NH_3): *m/z* 275.1 (M+2H).

Part D: 4-bromo-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde ethylene glycol acetal:

A mixture of part C material (1.75 g, 0.0064 moles) in benzene (150 mL) was treated with ethylene glycol (1.2 mL, 0.025 moles), pyridine (0.0035 moles) and p-toluenesulfonic acid mono hydrate (0.0035 moles). The

reaction mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 24 hours and TLC (1:50 MeOH / CH_2Cl_2) revealed a new spot at Rf=0.35 (visible under iodine). The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with 10 % sodium bicarbonate, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to furnish yellow oil. The crude was purified by flash column chromatography on silica gel using 25 % ethyl acetate / chloroform mixture to afford 1.96 g (97 %) white solid (mp 70-71 °C). ^1H NMR ($CDCl_3$): δ 0.78-0.89 (t, 6H, 2*CH_3), 1.29-1.36 (t, 3H, CH_3), 1.77-1.90 (m, 4H, 2*CH_2), 2.70-2.73 (q, 2H, CH_2), 3.98-4.3 (m, 5H, CH and 2*CH_2), 5.86 (s, 1H, CH). Mass spectrum (CI-NH_3): 317.1 (M^+). Anal. calcd. for $C_{13}H_{22}Br_1N_2O_2$: C, 49.22; H, 6.67; N, 8.83. Found: C, 49.43; H, 6.61; N, 8.78.

Part E: 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-ethyl)propyl-1H-imidazole-5-carboxaldehyde:
A solution of part D material (1.08 g, 0.0034 moles) in THF (20.0 mL) was cooled to - 78 °C and then a 1.6 M n-BuLi in hexane (2.4 mL, 0.004 moles) was added dropwise over 15 min under nitrogen atmosphere. The mixture was stirred at -78 °C for 2.5 h and then a solution of 2,4-dichlorobenzoyl chloride (0.84 g, 0.004 moles) in THF (5.0 mL) was added over 15 mins. The mixture was stirred at -78 °C for 6 h followed by room temperature overnight and TLC (30:70 EtOAc / hexane) showed a new spot at Rf= 0.43. The mixture was quenched with saturated NH_4Cl (10.0 ml), extracted with ethyl acetate (3*30 mL), washed with brine and dried ($MgSO_4$). The solvent was stripped off in vacuo to afford crude product which was purified by flash column chromatography on a silica gel using

15 % EtOAC / hexane to afford 0.61 g (44 % yield) of desired product as yellow oil. Mass spectrum (CI-NH_3): 411.2 (M^+). The acetal was dissolved in acetone (15.0 mL) and treated with a 3.0 M aqueous HCl solution (30.0 mL) at room temperature. The reaction mixture was stirred for 24 h at this temperature and TLC (30:70 EtOAc / hexane) showed a new spot at Rf=0.55. It was then quenched with saturated NaCl (50.0 ml), extracted with ethyl acetate (3*50 mL), washed with brine and dried ($MgSO_4$). The solvent was removed in vacuum to afford yellow liquid and purified the crude by flash column chromatography on a silica gel using 15 % EtOAC / hexane to afford 0.28 g (51 % yield) of desired product as yellow solid (mp 85-86 °C). ^1H NMR ($CDCl_3$): δ 0.785 (m, 6H, 2*CH_3), 1.28-1.33 (t, 3H, CH_3), 1.90-2.23 (m, 4H, 2*CH_2), 2.74-2.82 (q, 2H, CH_2), 3.98-4.05 (m, 1H, CH), 7.34-7.37 (d, 1H, aromatic), 7.45-7.46 (d, 1H, aromatic), 7.55-7.58 (d, 1H, aromatic). Mass spectrum (CI-NH_3): 367 (M^+). Anal. calcd. for $C_{18}H_{20}Cl_2N_2O_2$: C, 58.87; H, 5.50; N, 7.64. Found: C, 58.91; H, 5.60; N, 7.44.

Part F: Methyl 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-ethyl)propyl-imidazo-5-carboxylate

A mixture of Part E material (0.367 g, 0.001 moles) in methanol (60 mL) was reacted with NaCN (Aldrich, 0.245 g, 0.005 moles, 5 equiv.), AcOH (Baker, 96 mg; 0.0016 moles, 1.6 equiv.) and MnO_2, activated (Aldrich, 1.24 g, 0.021 moles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 18 h. TLC (1:50 MeOH/CH_2Cl_2) revealed absence of starting material spot at Rf=0.8 and showed a new spot at Rf=0.44. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo and the crude was purified by

flash column chromatography on a silica gel using 1:100 MeOH/CH_2Cl_2 as eluent to afford 320 mg (mp 73-74 °C, 81 %) of white solid after crystallization from hexane. Anal. calcd. for $C_{19}H_{22}Cl_2N_2O_3$: C,57.44; H,5.58; N,7.05. Found: C,57.31; H,5.45; N,6.85.

Part G: Title Compound

A mixture of Part F material (0.100 g, 0.00025 moles) in ethanol (10 mL) was treated with anhydrous hydrazine (0.105 g, 0.0033 moles) and refluxed under nitrogen for 48 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.35. The solvent was removed under vacuum and purified the crude by flash column chromatography on a silica gel using 15:85 EtOAc / hexane intially and then methanol to afford 70 mg (74 % yield) of the product as white solid after tituration of the oil with diethyl ether (mp 246-247 °C). HRMS calcd. for $C_{18}H_{21}Cl_2N_4O_1$: 379.1092. Found: 379.1070 (M+H).

Example 2 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-methyl)imidazo[4,5-d]pyridazin-7-one.

A mixture of Part F material of example 1 (0.100 g, 0.00025 moles) in ethanol (10 mL) was treated with anhydrous methylhydrazine (0.150 g, 0.0033 moles) and refluxed under nitrogen for 8 days. TLC (1:50 MeOH/CH_2Cl_2) showed a new spot at Rf=0.55. The solvent was removed under vacuum and purified the crude by flash column chromatography on a silica gel 1:50 MeOH/CH_2Cl_2 to afford 30 mg (31 % yield) of the product as white solid (mp 94-95 °C). HRMS calcd. for $C_{19}H_{23}Cl_2N_4O_1$: 393.1249. Found: 393.1250 (M+H).

Example 3 4-(2,4-dichlorophnyl)-2-ethyl-6-(N-ethyl)-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

To a solution of Part G of example 1 (0.1 g, 0.264 mmoles) in benzene (5.0 mL) was added n-tetrabutylammonium bromide (8.5 mg, 0.0264 mmoles), powdered KOH (15.0 mg, 0.264 mmoles) and iodoethane (0.124 g, 0.79 mmoles). The resultant mixture was stirred at room temperature under nitrogen for 20 h. TLC (1:50 $MeOH/CH_2Cl_2$) showed a new spot at Rf=0.73 along with disappearence of starting material (Rf=0.33). The reaction mixture was diluted with EtOAc (10 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 58 mg (54 % yield) of the product as colorless oil. HRMS calcd. for $C_{20}H_{25}N_4Cl_2O_1$: 407.1405. Found: 407.1404 (M+H).

Example 4 4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-propyl)-imidazo[4,5-d]pyridazin-7-one.

The title compound was prepared using Part G of example 1 material and 1-iodopropane and following the conditions outlined in example 3 to afford desired product as colorless oil (56mg, 51 % yield). Anal. calcd. for $C_{21}H_{26}N_4Cl_2O_1$: C, 59.86; H, 6.23; N, 13.30. Found: C,59.86 ; H,6.12 ; N, 13.13.

Example 5 6-(N-cyclopropylmethyl)-4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethyl)propyl-imidazo[4,5-d]pyridazin-7-one.

The title compound was prepared using Part G of example 1 material and bromomethylcyclopropane and following the conditions outlined in example 3 to

afford desired product as colorless oil (68 mg, 59 % yield). HRMS calcd. for $C_{22}H_{27}N_4Cl_2O_1$:433.1562. Found: 433.1563 (M+H).

Example 6 4-Bis(2,4-trifluoromethylphenyl)-2-ethyl-1-(1-ethyl)propyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one.

Part A: A solution of Part D material of example 1 in THF (30.0 mL) was cooled to -78 °C and then added dropwise 1.6 M n-BuLi in hexane over 15 mins. The mixture was stirred at -78 °C for 2 1/2 h and then added a solution of 2,4-$(CF_3)_2$-Ph-COCl in 5.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with a saturated NH_4Cl solution (50.0 ml), extracted with ethyl acetate (3*30 mL), the combined organic extracts were washed with brine and the solvent was removed under vacuum to afford an orange yellow liquid (4.3 g). TLC (30:70 EtOAc/hexane) of the crude showed absence of starting material spot (Rf=0.4) along with a new spot at Rf=0.47. The crude was purified by flash column chromatography on a silica gel using 30 % EtOAC/hexane to afford 1.53 g (mp 105-106 °C, 64 % yield) of desired benzoyl derivative as white solid. Mass spec. (CI-NH_3): 479.2 (M+H). Anal. calcd. for $C_{22}H_{24}N_2O_3F_6$: C, 55.23; H, 5.07; N, 5.87. Found; C, 54.96; H, 5.09; N, 5.72.

Part B: A solution of Part A material of example 6 (1.43 g, 2.9 mmoles) in acetone (30.0 mL)was cooled to 15 °C and then added 3M aq. HCl (60.0 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.63 along with disappearence of starting material

(Rf=0.43). The solvent was removed under vacuum, extracted with ethyl acetate (3*50 mL), washed with brine and stripped off the solvent in vacuum to afford yellow liquid. The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 1.03 g (82 % yield) of desired aldehyde as yellow liquid. Mass spec. (NH_3-CI): 435 (M+H). Anal. calcd. for $C_{20}H_{20}N_2O_2F_6$: C, 55.30; H, 4.64; N,6.46. Found; C,55.03; H,4.45; N,6.27.

Part C: A mixture of Part B material of example 6 (0.434 g, 1.0 mmole) in methanol (30 mL) was treated with NaCN (Aldrich, 0.245 g, 5.0 mmoles, 5 equiv.), AcOH (Baker, 96 mg; 1.6 mmoles, 1.6 equiv.) and MnO_2, activated (Aldrich, 1.24 g, 21.0 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 24 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at Rf=0.63 and showed a new spot at Rf=0.55. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 350 mg (mp 57-58 °C, 75 %) of pale yellow solid. Mass spec. (NH_3-CI): 465.3 (M+H). Anal. calcd. for $C_{21}H_{22}N_2O_3F_6$: C, 54.31; H, 4.79; N,6.03. Found: C,53.92; H,4.68; N, 5.80.

Part D: Title Compound:
A mixture of Part C material of example 6 (0.116 g, 0.250 mmoles) in ethylene glycol (3.0 mL) was treated with anhydrous methylhydrazine (0.15 g, Aldrich, 3.3

mmoles, 13 equiv.) and refluxed under nitrogen for 20 h. TLC (30:70 EtOAc/hexane) revealed both starting material and product had identical Rf values (0.55). The reaction mixture was cooled to room temperature and poured over 25 mL of water, extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford an oil which was crystallized from hexane to afford 16 mg (14 % yield; mp 139-140 °C) of white solid as desired product. HRMS calcd. for $C_{21}H_{23}N_4O_1F_6$: 461.1776. Found: 461.1763 (M+H).

Example 7 (±)-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

Part A: To a solution of 4,5-dibromo-2-ethyl-1-(2-pentyl)-1H-imidazole (37.5 g, 0.116 moles, prepared according to the method described in Part B of example 1) in THF (250 mL) was cooled to -78 °C and then a 1.6 M n-BuLi in hexane added dropwise (76.0 mL, 0.122 moles) over 45 mins. The mixture was stirred at -78 °C for 1h (brown solution) and then added DMF (27.0 g, 0.348 moles) dropwise over 30 mins. The mixture was stirred at -78 °C for 60 mins. The reaction mixture was quenched with saturated ammonium chloride (100 mL) at -78 °C and brought to room temperature. The reaction mixture was extracted with ethyl ether (3*100 mL), washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford 31.6 g of crude yellow oil. The crude was purified by flash column chromatography on a silica gel using chloroform as eluent to afford 18.5 g (59 % yield) of

desired aldehyde as colorless oil. Anal. calcd. for $C_{11}H_{17}N_2OBr$; C, 48.36; H, 6.27, N, 10.25. Found: C,48.64; H,6.01; N, 10.00.

Part B: A mixture of Part A material of example 7 (18.5 g, 0.068 moles) in benzene (250 mL) was treated with ethylene glycol (16.4 g, 0.264 moles), pyridine (2.7 g, 0.034 moles) and p-toluenesulfonic acid monohydrate (6.5 g, 0.034 moles). The reaction mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 36h. TLC (30:70 EtOAc/hexane) revealed a new spot at Rf=0.42 (visible under iodine) along with disappearence of starting material (Rf=0.54). The reaction mixture was cooled to room temperature, diluted with EtOAc (250 mL), washed with 10 % sodium bicarbonate (2*250 mL), brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to furnish acetal as white solid (20.7 g, mp 69-70 °C, 96 %). Mass spectrum (CI-NH_3): 317.1 (M^+). Anal. calcd. for $C_{13}H_{22}N_2O_2Br_1$; C,49.22; H, 6.67, N, 8.83. Found: C,49.38; H,6.62; N, 8.68.

Part C: A solution of Part B material of example 7 (2.73 g, 0.01moles) in THF (30 mL) was cooled to - 78 °C and then added dropwise 1.6 M n-BuLi in hexane (7.4 mL) over 15 mins. The mixture was stirred at -78°C for 2 1/2 h and then added a solution of 2,4-dichlorobenzoyl chloride in 5.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with satd. NH_4Cl (50.0 ml), extracted with ethyl acetate (3*30 mL), washed with brine and stripped off the solvent in vacuum to afford orange yellow liquid (4.3 g). TLC (30:70

EtOAc/hexane) of the crude showed absence of starting material spot (Rf=0.4) and a new spot at Rf= 0.47. The crude was purified by flash column chromatography on a silica gel using 30 % EtOAC/hexane to afford 2.4 g (mp 129-130 °C, 59 % yield) of benzoyl derivative as white solid. Mass spec. (CI-NH3): 411 (M^+). Anal. calcd. for $C_{20}H_{24}N_2O_3Cl_2$: C, 58.40; H, 5.88; N, 6.81. Found: C, 58.45; H, 5.95; N, 6.68.

Part D: A solution of Part C material of example 7 (2.3 g, 0.056 moles) in acetone (60 mL) was cooled to 15 °C and then added 3M aq. HCl (120 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.58 along with disappearence of starting material (Rf=0.43). The solvent was removed under vacuum, extracted with ethyl acetate (3*50 mL), washed with brine and stripped off the solvent in vacuum to afford yellow liquid (2.4 g). The crude was purified by flash column chromatography on a silica gel using dichloromethane as eluent to afford 1.46 g (71 % yield) of keto aldehyde derivative as yellow solid (mp 43-44 °C). Mass spec. (NH_3-CI): 367 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_2Cl_2$: C, 58.87; H, 5.50; N,7.64. Found: C,58.96; H,5.34; N,7.46.

Part E : A mixture of Part D material of example 7(1.0 g, 0.0027 moles) in methanol (50 mL) was treated with NaCN (Aldrich, 0.67 g, 0.0136 moles, 5 equiv.), AcOH (Baker, 260 mg; 0.00432 moles, 1.6 equiv.) and MnO_2, activated (Aldrich, 3.34 g, 0.057 moles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 20 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at Rf=0.58 and showed a new spot at Rf=0.4. The

reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford 0.98 g of yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 910 mg (85 %) of keto ester derivative as yellow oil. Mass spec.: 397.2 (M^+). Anal. calcd. for $C_{19}H_{22}N_2O_3Cl_2$: C,57.44; H,5.58; N,7.05. Found: C, 57.25; H, 5.70; N, 6.80.

Part F: Title Compound: A mixture of Part E material of example 7 (0.100 g, 0.00025 moles) in ethylene glycol (2 mL) was treated with anhydrous methylhydrazine (0.105 g, 0.0033 moles) and refluxed under nitrogen for 4 h. TLC (30:70 EtOAc/hexane) revealed a new spot (Rf=0.44) along with disappearence of starting material (Rf=0.4. The reaction mixture was cooled to room temp and poured over 25 mL of water, extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc/hexane to afford colorless oil which was crystallized from hexane to afford 42 mg of white solid (43 %, mp 89-90 °C). Mass spec. (CI-NH_3): 393.2 (M^+). Anal. calcd. for $C_{19}H_{22}N_4Cl_2O$: C, 58.02; H, 5.65; N, 14.24. Found: C,58.32; H, 5.59; N, 14.14.

Example 8 (±)-4-(2,4-dichlorophenyl)-2-ethyl-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

A mixture of Part E material of example 7 (0.460 g, 0.00115 moles) in ethylene glycol (5 mL) was treated with anhydrous hydrazine (0.48 g, 0.0151 moles) and refluxed under nitrogen for 4 h. TLC

(30:70 EtOAc/hexane) revealed a new spot (Rf=0.44) along with disappearence of starting material (Rf=0.4). The reaction mixture was cooled to room temp and poured over 25 mL of water, extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 15 % EtOAc/hexane to afford colorless oil which was crystallized from hexane to afford 310 mg of white solid (71 %, mp 217-18 °C). Mass spec. (CI-NH_3):379.2 (M^+). Anal. calcd. for $C_{18}H_{20}N_4Cl_2O$: C, 57.00; H,5.33; N,14.77. Found: C,57.02; H, 5.35; N, 14.59.

Example 9 (±)-4-(2,5-dimethyl-4-methoxyphenyl)-2-ethyl-6-(N-methyl)-1-(1-methyl)butyl-imidazo[4,5-d]pyridazin-7-one.

Part A: Synthesis of 2,5-dimethyl-4-methoxybenzoyl chloride: To a stirred mixture of 2,5-dimethyl-4-methoxybenzaldehyde (6.7 g, 0.004 moles) in acetone (140 mL) at 60 °C was added $KMnO_4$ (8.46 g, 0.0054 moles) dissolved in water (250 mL) dropwise over 30 mins. The reaction mixture quickly turned into brown suspended solution. The reaction mixture was further continued for 1h. The reaction mixture was cooled to room temp., filtered through celite and extracted with diethyl ether. The aq. layer was acidified with con. HCl, filtered the white solid separated, washed with water and dried at 50 °C for 30 mins under vacuum to afford 3.46 g of carboxylic acid as white solid (mp 161-162 °C, 48 % yield). The carboxylic acid (3.4 g, 0.0189 moles) was dissolved in 75 mL of anhydrous benzene and added few drops of pyridine followed by addition of thionyl chloride (5.0 mL, 0.0689, 3.65 equiv., fw 118.97, d 1.631).

The resultant mixture was refluxed at reflux for 20 h. The solvent was removed under vacuum, the solid thus resulted was treated with 5.0 mL of hexane and filtered the undissolved white solid (3.7 g, mp 84-85 °C, 98.7 %).

Part B: A solution of Part B material of example 7 (2.73 g, 0.01 moles) in THF was cooled to - 78 °C and then added dropwise 1.6 M n-BuLi in hexane (7.4 mL, 0.0115 moles) over 15 mins. The mixture was stirred at -78 °C for 2 1/2 h and then added a solution of 2,5-$(Me)_2$-4-OMe-Ph-COCl (2.2 g, 0.012 moles) in 10.0 mL of THF over 15 mins. The mixture was stirred at -78°C for 6 h and then warm to room temp and stirred overnight. The reaction mixture was quenched with satd. NH_4Cl (50.0 ml), extracted with ethyl acetate (3*30 mL), washed with brine and stripped off the solvent in vacuum to afford orange yellow liquid. TLC (30:70 EtOAc/hexane) of the crude showed absence of starting material spot (Rf=0.4) along with product spot appeared at Rf=0.38. The crude was purified by flash column chromatography on a silica gel using 15 % EtOAC/hexane to afford 1.53 g (mp 160-162 °C, 38 % yield) of desired benzoyl derivative as pale yellow solid. Mass spec. (CI-NH_3): 401.3 (M+H). Anal. calcd. for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found; C, 69.05; H, 8.10; N, 6.33.

Part C: A solution of Part B material of example 9 (1.4 g, 0.0035 moles) in acetone (30 mL) was cooled to 15 °C and then added 3M aq. HCl (60 mL) over 15 mins. The mixture was stirred below 30 °C for 24 h. TLC (30:70 EtOAc/hexane) showed product spot at 0.56. The solvent was removed under vacuum, extracted with ethyl acetate (3*50 mL), washed with brine and

stripped off the solvent in vacuum to afford yellow liquid. The crude was purified by flash column chromatography on a silica gel using dichloromethane, followed by 1% MeOH/dichloromethane as eluents to afford 0.48 g (39 % yield) of desired product as yellow liquid. HRMS calcd. for $C_{21}H_{29}N_2O_3$:357.2178. Found:357.2169 (M+H).

Part D: A mixture of Part C material of example 9 (0.357 g, 1.0 mmole) in methanol (30 mL) was treated with NaCN (Aldrich, 0.245 g, 5.0 Mmoles, 5 equiv.), AcOH (Baker, 96 mg; 1.6 mmoles, 1.6 equiv.) and MnO_2, activated (Aldrich, 1.24 g, 21.0 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 24 h. TLC (30:70 EtOAc/hexane) revealed absence of starting material at Rf=0.56 and showed a new spot at Rf=0.30. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc/hexane as eluent to afford 205 mg (53 %) of ketoester derivative as pale yellow oil. HRMS calcd. for $C_{22}H_{30}N_2O_4$: 386.2205. Found: 387.2264 (M+H).

Part E: A mixture of Part D material of example 9 (0.100 g, 0.000259 moles) in ethylene glycol (3.0 mL) was treated with anhydrous methylhydrazine (0.15 g, Aldrich, 0.0033 moles, 13 equiv.) and refluxed under nitrogen for 14 h. TLC (30:70 EtOAc/hexane) revealed a new spot (Rf=0.40) along with disappearence of starting material (Rf=0.3). The reaction mixture was cooled to room temp and poured over 25 mL of water,

extracted with EtOAc (3*15 mL), washed with brine and dried. The solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 30 % EtOAc/hexane to afford 43 mg (43 % yield) of a solid: HRMS calcd. for $C_{22}H_{31}N_4O_2$: 383.2447. Found: 383.2433 (M+H).

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

The examples delineated in Tables 1, 2, 3 and 4 may be prepared by the methods outlined in Examples 1, 2 or 3 or combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, amorph. is amorphous.

EXAMPLE 544

4-(2,4-Dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

Part A: Synthesis of 1-[(Benzyloxy)methyl]4,5-dibromo-2-ethylimidazole: To a mechanically stirred solution of 4,5-dibromo-2-ethylimidazole (25.4 g, 0.1 mole,) in anhydrous DMF (250 mL) was treated with K_2CO_3 (69.1 g, fw=138.2, 0.5 moles, 5 equiv.) followed by dropwise addition of benzyl chloromethyl ether (18.5 g, 0.11 moles, 93 % pure, TCI, fw=156.61) and stirred overnight at room temp under nitrogen for 20 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material imidazole (Rf=0.2) along with formation of product (Rf=0.71). The reaction mixture was filtered, washed the solid with dichloromethane and the combined filterate was evaporated under reduced pressure and purified the crude (47 g) by flash column chromatography (dichloromethane eluent) to afford 31.75 g (85 %) of colorless oil. Mass spectrum (m/z=375, M+H).

Part B: Synthesis of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formylimidazole: A solution of 1-[(Benzyloxy)methyl]-4,5-dibromo-2-ethylimidazole (28.0 g, 75.0 mmol, Part A of example 544) in THF (300 mL) was cooled to - 78 °C under nitrogen atmosphere and then added dropwise 1.6 M n-BuLi in hexane (51.75 mL, 82.5 mmol, Aldrich) over 30 mins. The mixture was stirred at -78 °C for 30 mins and then added DMF (16.5 g, 225 mmol, Aldrich) dropwise over 15 mins. The mixture was stirred at -78 °C for 30 mins. A small portion of the reaction mixture was quenched with satd. NH_4Cl at -78 °C. TLC (30:70 EtOAc/hexane) revealed both starting material and product showed almost identical Rf values (0.71 & 0.70) along with another minor spot at Rf=0.15. However, mass spectrum (CI-NH_3) revealed absence of starting material and formation of product (m/z=325, M+2H). The reaction mixture was quenched with satd. ammonium chloride (20 mL) at -78 °C and brought to room temp. The reaction mixture was extracted with ethyl acetate (3 x 100 mL), washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford crude yellow oil. The crude was purified by flah column chromatography on a silica gel using dichloromethane

as eluent to afford 22.6 g (93 %) of colorless oil. HRMS calcd. for $C_{14}H_{16}N_2O_2Br$: 323.0395. Found:323.0394 (M+H).

Part C: 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formylimidazole ethylene acetal: A mixture of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formyl-imidazole (22.6 g, 0.0699 moles) in benzene (400 mL) was treated with ethylene glycol (16.9 g, 0.273 moles, fw 62, 3.9 equiv.), pyridine (2.76 g, 0.03495 moles, fw=79.1, 0.5 equiv.) and p-toluenesulfonic acid monohydrate (6.6 g, 0.03495moles, fw=190, 0.5 equiv). The reaction mixture was heated at reflux in a 20 mL capacity Dean-Stark trap equipped apparatus for 24 hours. TLC (30:70 EtOAc / hexane) revealed a new spot at Rf=0.35 (visible under iodine) along with disappearence of starting material (Rf=0.70). The reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL), washed with 10 % sodium bicarbonate, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to furnish yellow oil. The crude was purified by flash column chromatography on silica gel using 25 % ethyl acetate / hexane mixture to afford 22.8 g (89 %) colorless oil. ^1H NMR ($CDCl_3$): 1.29-1.33 (t, 3H, CH_3), 2.71-2.78 (q, 2H, CH_2), 3.96 (s, 4H, 2 x OCH_2), 4.55 (s, 2H, CH_2), 5.4 (S, 2H, CH_2), 5.88 (S, 1H, CH), 7.27-7.38 (M, 5H, aromatic). HRMS calcd. for $C_{16}H_{20}N_2O_3Br_1$: 367.0658. Found: 367.0653 (M+H).

Part D: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-formylimidazole ethylene acetal: A solution of 1-[(Benzyloxy)methyl]-4-bromo-2-ethyl-5-formyl-imidazole ethylene acetal (22.5 g, 0.0613 moles, fw=367.25, Part C of Example 544) in THF (200.0 mL) was cooled to - 78 °C and then added dropwise 1.6 M n-BuLi in hexane (43.7 mL, 0.071 moles, 1.1 equiv.) over 15 mins under nitrogen atmosphere. The mixture was stirred at -78°C for 90 mins and then added a solution of 2,4-dichlorobenzoyl chloride (14.3 g, 0.071 moles, 1.1 equiv.) in THF (5.0 mL) over 15 mins. The mixture was stirred at -78°C for 4 h followed by room temperature overnight .TLC (30:70 EtOAc / hexane) showed a new spot at Rf= 0.38 along with disappearence of starting material (Rf=0.35). The mixture was quenched with saturated NH_4Cl (100.0 ml), extracted with ethyl acetate (3 x 150 mL), washed with brine and dried ($MgSO_4$). The solvent was stripped off in vacuo

to afford crude product (yellow oil) which was purified by flash column chromatography on a silica gel using 20 % EtOAC / hexane to afford 12.3 g (mp 95-96 °C , 43 % yield) of desired product as white solid. ^{1}H NMR ($CDCl_3$): 1.22-1.27 (t, 3H, CH_3), 2.74-2.81 (q, 2H, CH_2), 3.94-4.03 (m, 4H, 2 x OCH_2), 4.59 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 6.62 (s, 1H, CH), 7.27-7.54 (m, 8H, aromatic). Mass spectrum (CI-NH_3): 461 (M^+). Anal. calcd. for $C_{23}H_{22}N_2O_4Cl_2$: C, 59.88; H, 4.82; N, 6.07. Found: C, 59.77; H, 4.78; N, 5.93.

Part E: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-formylimidazole : The above acetal (12.1 g, 0.0263 moles, Part D of Example 544) was dissolved in acetone (200.0 mL) and treated with 3.0 M aqeous HCl (400.0 mL) at room temperature. The reaction mixture was stirred for 24 h at this temperature and TLC (30:70 EtOAc / hexane) showed a new spot at Rf=0.55. It was then quenched with saturated NaCl (50.0 ml), extracted with ethyl acetate (3 x 150 mL), washed with brine and dried ($MgSO_4$). The solvent was removed in vacuum to afford yellow liquid and purified the crude by flash column chromatography on a silica gel using 15 % EtOAC / hexane to afford 6.0 g (55 % yield) of desired product as colorless oil. ^{1}H NMR ($CDCl_3$): 1.27-1.32 (t, 3H, CH_3), 2.78-2.86 (q, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.92 (s, 2H, CH_2), 7.25-7.55 (m, 8H, aromatic), 10.39 (s, 1H, CHO). Mass spectrum (CI-NH_3): 417 (M^+). Anal. calcd. for $C_{21}H_{18}N_2O_3Cl_2$: C, 60.44; H, 4.36; N, 6.71. Found: C, 60.43; H, 4.45; N, 6.49.

Part F: Methyl 1-[(Benzyloxy)methyl]-4-(2,4-dichlorobenzoyl)-2-ethyl-5-imidazole carboxylate: A mixture of 2-Et-5-CHO-imidazole derivative (6.0 g, fw=417, 14.34 mmoles, Part E of Example 544) in methanol (120 mL) was treated with NaCN (Aldrich, fw=49, 3.54 g, 12.0 mmoles, 5 equiv.), AcOH (Baker, fw = 60, 1.38 g; 22.92 mmoles, 1.6 equiv.) and MnO_2, activated (Aldrich, fw=86.94, 25.8 g, 301.2 mmoles, 21 equiv.). The resulting mixture was stirred at room temp under nitrogen for 3 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material at Rf=0.55 and showed a new spot at Rf=0.35. The reaction mixture was filtered through celite, washed with methanol, concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried and concentrated in vacuo to

afford yellow oil. The crude was purified by flash column chromatography on a silica gel using 30:70 EtOAc / hexane as eluent to afford 4.62 g (72 % yield) of colorless oil. HRMS calcd. for $C_{22}H_{21}Cl_2N_2O_4$: 447.0878. Found: 447.0870 (M+H). Anal. calcd. for $C_{22}H_{20}Cl_2N_2O_4$: C, 59.07; H, 4.52; N, 6.26. Found: C, 58.97; H, 4.65; N, 6.07

Part G: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-imidazo[4,5-d]pyridazin-7-one: A mixture of imidazole deriv. (3.55 g, fw=447, 0.00794 moles, Part F of Example 544) in ethanol (50 mL) was treated with anhydrous hydrazine (3.3 g, 0.102 moles, 13 equiv) and refluxed under nitrogen for 2 h. TLC (30:70 EtOAc / hexane) revealed absence of starting material (Rf=0.35) and showed a new spot (Rf=0.27). The solvent was removed under vacuo and purified the crude titurating with 1:1 EtOH / hexane to afford 2.2 g (65 % yield, mp 174-175 °C) of desired product as white solid. Mass spectrum (APcI): (m/z=429, M^+). Anal. calcd. for $C_{21}H_{18}N_4Cl_2O_2$: C, 58.75; H, 4.24; N, 13.05. Found: C, 58.65; H, 4.30; N, 12.86.

Part H: 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one: To a solution of the above 6H-imidazo[4,5-d]pyridazin-7-one derivative (2.2 g, 0.005 moles, Part G of Example 544) in benzene (100 mL) was added powdered KOH (0.43 g, 0.0076 moles), n-Bu_4NBr (161 mg, 0.0005 moles) and MeI (excess) at room temperature. The reaction mixture appeared white suspension and stirred for 48 h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.40 along with disappearence of starting material (Rf=0.27). The reaction mixture was diluted with EtOAc (50 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 25:75 EtOAc / hexane as eluent to afford 1.96 g (86 % yield, mp 80-81 °C) of the product as white solid. Anal. calcd. for $C_{21}H_{20}N_4Cl_2O_2$: C, 59.60; H, 4.56; N, 12.64. Found: C, 59.61; H, 4.57; N, 12.52.

Part I: Title Compound: A mixture of 1-[(Benzyloxy)methyl]-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one (2.6 g, fw=443.33, 5.87 mmol, Part H of Example 544) in ethanol (100 mL) was treated with conc. HCl (2.93 mL,

29.3 mmol, 5.0 equiv) and refluxed under nitrogen for 60 mins. TLC (30:70 EtOAc/hexane) revealed disappearence of starting material (Rf=0.40) and a new spot appeared near the origin. The reaction mixture was cooled to room temperature adjusted the pH using $NaHCO_3$ and the solvent was removed under vacuo and purified the crude by flash column chromatography on a silica gel using 50 % EtOAc / hexane to afford 1.85 g (mp 234-235 °C, 97 % yield) of desired product as white solid. NMR ($CDCl_3$): 1.46-1.52 (t, 3H, CH_3), 3.04-3.11 (q, 2H, CH_2), 4.04 (s, 3H, N-Me), 7.38-7.41 (d, 2H, aromatic), 7.54-7.57 (m, 3H, aromatic), 13.65 (bs, 1H, NH). Mass spectrum (CI-NH_3): m/z=323 (M^+). HRMS calcd. for $C_{14}H_{13}N_4Cl_2O_1$: 323.0466. Found:323.0477 (M+H). Anal. calcd. for $C_{14}H_{12}N_4Cl_2O_1$: C, 52.03; H, 3.74. Found: C, 51.92 ; H, 4.07.

EXAMPLE 546

1-Butyl-4-(2,4-dichlorophenyl)-2-ethyl-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

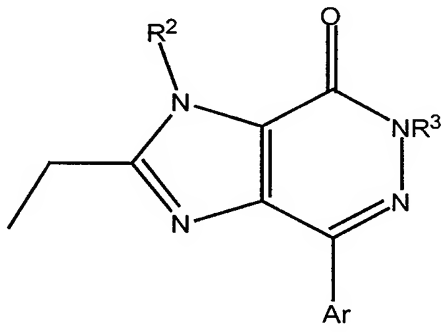
To a solution of imidazopyridazin-7-one deriv. (32.3 mg, fw=323, 0.1 mmol, Part I of example 544) in DMF (2.0 mL) under nitrogen atmosphere was added 60 % NaH in oil dispersion (6.0 mg, fw=24, 0.15 mmol, 1.5 equiv.). The mixture was stirred at room temp for 5 mins and then added 1-bromobutane (27.6 mg, fw=184, 0.15 mmol, 1.5 equiv) to reaction mixture and stirred overnight. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.36 along with disappearence of starting material (Rf=origin). The reaction mixture was diluted with water (5.0 mL), extracted with EtOAc (3*5 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 25:75 EtOAc/hexane as eluent to afford 29.7 mg (78 % yield) of the product as colorless oil. HRMS calcd. for $C_{18}H_{21}N_4O_1Cl_2$: 379.1092. Found: 379.1086 (M+H).

EXAMPLE 548

4-(2,4-dichlorophenyl)-2-ethyl-1-[1-(ethyl)pentyl)]-6-(N-methyl)-imidazo[4,5-d]pyridazin-7-one

To a solution of imidazopyridazin-7-one deriv. (48.3 mg, fw=323, 0.15 mmol, Part I of Example 544) in THF (2.0 mL) under nitrogen atmosphere was added PPh_3 (43.3 mg, fw=262.29, 0.165 mmol, 1.1 equiv.), and 3-heptanol (21.0 mg, Aldrich, 0.18 mmol, fw=116.2, 1.2 equiv.). The mixture was cooled to -20 °C and then added diisopropylazodicarboxylate (33.3 microlit., Aldrich, 0.165 mmol, fw=202, 1.1 equiv.) dropwise using a syringe. The resultant mixture was stirred at -20 °C for 2 h followed by room temperature for 20h. TLC (30:70 EtOAc/hexane) showed a new spot at Rf=0.53 along with trace amount of starting material (Rf=origin). The reaction mixture was concentrated to a residue. The crude was purified by flash column chromatography on a silica gel using 15:85 EtOAc/hexane as eluent to afford 37 mg (58 % yield, 110-111 °C) of the product as white solid. HRMS calcd. for $C_{21}H_{27}N_4O_1Cl_2$: 421.1562. Found:421.1555 (M+H).

Table 1



Ex.	R_3	R_2	Ar	mp (°C)
2	Me	3-pentyl	2,4-Cl_2-Ph	94-95
3	Et	3-pentyl	2,4-Cl_2-Ph	oil
4	Pr	3-pentyl	2,4-Cl_2-Ph	oil
5	CH_2-c-C_3H_5	3-pentyl	2,4-Cl_2-Ph	oil
6	Me	3-pentyl	2,4-$(CF_3)_2$-Ph	139-140
7	Me	2-pentyl	2,4-Cl_2-Ph	89-90
9	Me	2-pentyl	2,5-$(Me)_2$-4-MeO-Ph	amorph.

	10	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
	12	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
	13	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
	14	Me	2-butyl	2,4-Cl_2-Ph	
5	15	Me	cyclobutyl	2,4-Cl_2-Ph	oil
	16	Me	cyclopentyl	2,4-Cl_2-Ph	180-181
	17	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
	18	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	oil
	19	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
10	20	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	117-118
	21	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
	22	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	
	23	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph	
	24	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph	
15	25	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph	
	26	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph	
	27	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph	
	28	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph	
	29	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph	
20	30	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph	
	31	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph	140-142
	32	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph	
	33	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Cl_2-Ph	
	34	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph	
25	35	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph	
	36	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph	
	37	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph	
	38	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph	
	39	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph	
30	40	Me	CH($CH_2C{=}CMe$)Et	2,4-Cl_2-Ph	
	41	Me	CH($CH_2CH{=}CHMe$)Et	2,4-Cl_2-Ph	
	42	Me	CH(Et)CH_2OH	2,4,6-Me_3-Ph	
	43	Me	CH(Et)CH_2OMe	2,4,6-Me_3-Ph	
	44	Me	CH(Et)CH_2CH_2OMe	2,4,6-Me_3-Ph	
35	45	Me	3-pentyl	2,4,6-Me_3-Ph	

	46	Me	2-pentyl	2,4,6-Me_3-Ph
	47	Me	2-butyl	2,4,6-Me_3-Ph
	48	Me	cyclobutyl	2,4,6-Me_3-Ph
	49	Me	cyclopentyl	2,4,6-Me_3-Ph
5	50	Me	CH(Me)cyclobutyl	2,4,6-Me_3-Ph
	51	Me	CH(Me)cyclopropyl	2,4,6-Me_3-Ph
	52	Me	CH(OMe)cyclopropyl	2,4,6-Me_3-Ph
	53	Me	CH(Et)cyclobutyl	2,4,6-Me_3-Ph
	54	Me	CH(Et)cyclopropyl	2,4,6-Me_3-Ph
10	55	Me	CH(Me)CH_2-cyclobutyl	2,4,6-Me_3-Ph
	56	Me	CH(Me)CH_2-cyclopropyl	2,4,6-Me_3-Ph
	57	Me	CH(OMe)CH_2-cyclopropyl	2,4,6-Me_3-Ph
	58	Me	CH(Et)CH_2-cyclobutyl	2,4,6-Me_3-Ph
	59	Me	CH(Et)CH_2-cyclopropyl	2,4,6-Me_3-Ph
15	60	Me	CH(CH_2OMe)cyclobutyl	2,4,6-Me_3-Ph
	61	Me	CH(CH_2OMe)cyclopropyl	2,4,6-Me_3-Ph
	62	Me	CH(CH_2OEt)cyclobutyl	2,4,6-Me_3-Ph
	63	Me	CH(CH_2OEt)cyclopropyl	2,4,6-Me_3-Ph
	64	Me	CH(cyclobutyl)$_2$	2,4,6-Me_3-Ph
20	65	Me	CH(cyclopropyl)$_2$	2,4,6-Me_3-Ph
	66	Me	CH(Et)CH_2CONMe_2	2,4,6-Me_3-Ph
	67	Me	CH(Et)$CH_2CH_2NMe_2$	2,4,6-Me_3-Ph
	68	Me	CH(CH_2OMe)Me	2,4,6-Me_3-Ph
	69	Me	CH(CH_2OMe)Et	2,4,6-Me_3-Ph
25	70	Me	CH(CH_2OMe)Pr	2,4,6-Me_3-Ph
	71	Me	CH(CH_2OEt)Me	2,4,6-Me_3-Ph
	72	Me	CH(CH_2OEt)Et	2,4,6-Me_3-Ph
	73	Me	CH(CH_2OEt)Pr	2,4,6-Me_3-Ph
	74	Me	CH($CH_2C{=}CMe$)Et	2,4,6-Me_3-Ph
30	75	Me	CH($CH_2CH{=}CHMe$)Et	2,4,6-Me_3-Ph
	76	Me	CH(Et)CH_2OH	2,4-Me_2-Ph
	77	Me	CH(Et)CH_2OMe	2,4-Me_2-Ph
	78	Me	CH(Et)CH_2CH_2OMe	2,4-Me_2-Ph
	79	Me	3-pentyl	2,4-Me_2-Ph
35	80	Me	2-pentyl	2,4-Me_2-Ph

	81	Me	2-butyl	2,4-Me_2-Ph	
	82	Me	cyclobutyl	2,4-Me_2-Ph	
	83	Me	cyclopentyl	2,4-Me_2-Ph	
	84	Me	CH(Me)cyclobutyl	2,4-Me_2-Ph	
5	85	Me	CH(OH)cyclobutyl	2,4-Me_2-Ph	
	86	Me	CH(Me)cyclopropyl	2,4-Me_2-Ph	
	87	Me	CH(OH)cyclopropyl	2,4-Me_2-Ph	
	88	Me	CH(Et)cyclobutyl	2,4-Me_2-Ph	
	89	Me	CH(Et)cyclopropyl	2,4-Me_2-Ph	
10	90	Me	CH(Me)CH_2-cyclobutyl	2,4-Me_2-Ph	
	91	Me	CH(Me)CH_2-cyclopropyl	2,4-Me_2-Ph	
	92	Me	CH(OMe)CH_2-cyclopropyl	2,4-Me_2-Ph	
	93	Me	CH(Et)CH_2-cyclobutyl	2,4-Me_2-Ph	
	94	Me	CH(Et)CH_2-cyclopropyl	2,4-Me_2-Ph	
15	95	Me	CH(CH_2OMe)cyclobutyl	2,4-Me_2-Ph	
	96	Me	CH(CH_2OMe)cyclopropyl	2,4-Me_2-Ph	
	97	Me	CH(CH_2OEt)cyclobutyl	2,4-Me_2-Ph	
	98	Me	CH(CH_2OEt)cyclopropyl	2,4-Me_2-Ph	
	99	Me	CH(cyclobutyl)$_2$	2,4-Me_2-Ph	
20	100	Me	CH(cyclopropyl)$_2$	2,4-Me_2-Ph	
	101	Me	CH(Et)CH_2CONMe_2	2,4-Me_2-Ph	
	102	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Me_2-Ph	
	103	Me	CH(CH_2OMe)Me	2,4-Me_2-Ph	
	104	Me	CH(CH_2OMe)Et	2,4-Me_2-Ph	
25	105	Me	CH(CH_2OMe)Pr	2,4-Me_2-Ph	
	106	Me	CH(CH_2OEt)Me	2,4-Me_2-Ph	
	107	Me	CH(CH_2OEt)Et	2,4-Me_2-Ph	
	108	Me	CH(CH_2OEt)Pr	2,4-Me_2-Ph	
	109	Me	CH($CH_2C{=}CMe$)Et	2,4-Me_2-Ph	
30	110	Me	CH($CH_2C{=}CMe$)Et	2,4-Me_2-Ph	
	111	Me	CH(Et)CH_2OH	2-Me-4-MeO-Ph	
	112	Me	CH(Et)CH_2OMe	2-Me-4-MeO-Ph	
	113	Me	CH(Et)CH_2CH_2OMe	2-Me-4-MeO-Ph	
	114	Me	3-pentyl	2-Me-4-MeO-Ph	125-126
35	115	Me	2-pentyl	2-Me-4-MeO-Ph	oil

	116	Me	2-butyl	2-Me-4-MeO-Ph	
	117	Me	cyclobutyl	2-Me-4-MeO-Ph	
	118	Me	cyclopentyl	2-Me-4-MeO-Ph	
	119	Me	CH(Me)cyclobutyl	2-Me-4-MeO-Ph	
5	120	Me	CH(Me)cyclopropyl	2-Me-4-MeO-Ph	
	121	Me	CH(Et)cyclobutyl	2-Me-4-MeO-Ph	
	122	Me	CH(Et)cyclopropyl	2-Me-4-MeO-Ph	
	123	Me	$CH(Me)CH_2$-cyclobutyl	2-Me-4-MeO-Ph	
	124	Me	$CH(Me)CH_2$-cyclopropyl	2-Me-4-MeO-Ph	
10	125	Me	$CH(Et)CH_2$-cyclobutyl	2-Me-4-MeO-Ph	
	126	Me	$CH(Et)CH_2$-cyclopropyl	2-Me-4-MeO-Ph	
	127	Me	$CH(CH_2OMe)$cyclobutyl	2-Me-4-MeO-Ph	
	128	Me	$CH(CH_2OMe)$cyclopropyl	2-Me-4-MeO-Ph	
	129	Me	$CH(CH_2OEt)$cyclobutyl	2-Me-4-MeO-Ph	
15	130	Me	$CH(CH_2OEt)$cyclopropyl	2-Me-4-MeO-Ph	
	131	Me	$CH(cyclobutyl)_2$	2-Me-4-MeO-Ph	
	132	Me	$CH(cyclopropyl)_2$	2-Me-4-MeO-Ph	
	133	Me	$CH(Et)CH_2CONMe_2$	2-Me-4-MeO-Ph	
	134	Me	$CH(Et)CH_2CH_2NMe_2$	2-Me-4-MeO-Ph	
20	135	Me	$CH(CH_2OMe)Me$	2-Me-4-MeO-Ph	
	136	Me	$CH(CH_2OMe)Et$	2-Me-4-MeO-Ph	
	137	Me	$CH(CH_2OMe)Pr$	2-Me-4-MeO-Ph	
	138	Me	$CH(CH_2OEt)Me$	2-Me-4-MeO-Ph	
	139	Me	$CH(CH_2OEt)Et$	2-Me-4-MeO-Ph	
25	140	Me	$CH(CH_2OEt)Pr$	2-Me-4-MeO-Ph	
	141	Me	$CH(CH_2C{\equiv}CMe)Et$	2-Me-4-MeO-Ph	
	142	Me	$CH(CH_2CH{=}CHMe)Et$	2-Me-4-MeO-Ph	
	143	Me	$CH(Et)CH_2OH$	2-Cl-4-MeO-Ph	
	144	Me	$CH(Et)CH_2OMe$	2-Cl-4-MeO-Ph	
30	145	Me	$CH(Et)CH_2CH_2OMe$	2-Cl-4-MeO-Ph	
	146	Me	3-pentyl	2-Cl-4-MeO-Ph	
	147	Me	2-pentyl	2-Cl-4-MeO-Ph	112-113
	148	Me	2-butyl	2-Cl-4-MeO-Ph	
	149	Me	cyclobutyl	2-Cl-4-MeO-Ph	
35	150	Me	cyclopentyl	2-Cl-4-MeO-Ph	

151	Me	CH(Me)cyclobutyl	2-Cl-4-MeO-Ph
152	Me	CH(Me)cyclopropyl	2-Cl-4-MeO-Ph
153	Me	CH(Et)cyclobutyl	2-Cl-4-MeO-Ph
154	Me	CH(Et)cyclopropyl	2-Cl-4-MeO-Ph
155	Me	$CH(Me)CH_2$-cyclobutyl	2-Cl-4-MeO-Ph
156	Me	$CH(Me)CH_2$-cyclopropyl	2-Cl-4-MeO-Ph
157	Me	$CH(Et)CH_2$-cyclobutyl	2-Cl-4-MeO-Ph
158	Me	$CH(Et)CH_2$-cyclopropyl	2-Cl-4-MeO-Ph
159	Me	$CH(CH_2OMe)$cyclobutyl	2-Cl-4-MeO-Ph
160	Me	$CH(CH_2OMe)$cyclopropyl	2-Cl-4-MeO-Ph
161	Me	$CH(CH_2OEt)$cyclobutyl	2-Cl-4-MeO-Ph
162	Me	$CH(CH_2OEt)$cyclopropyl	2-Cl-4-MeO-Ph
163	Me	$CH(cyclobutyl)_2$	2-Cl-4-MeO-Ph
164	Me	$CH(cyclopropyl)_2$	2-Cl-4-MeO-Ph
165	Me	$CH(Et)CH_2CONMe_2$	2-Cl-4-MeO-Ph
166	Me	$CH(Et)CH_2CH_2NMe_2$	2-Cl-4-MeO-Ph
167	Me	$CH(CH_2OMe)Me$	2-Cl-4-MeO-Ph
168	Me	$CH(CH_2OMe)Et$	2-Cl-4-MeO-Ph
169	Me	$CH(CH_2OMe)Pr$	2-Cl-4-MeO-Ph
170	Me	$CH(CH_2OEt)Me$	2-Cl-4-MeO-Ph
171	Me	$CH(CH_2OEt)Et$	2-Cl-4-MeO-Ph
172	Me	$CH(CH_2OEt)Pr$	2-Cl-4-MeO-Ph
173	Me	$CH(CH_2C{\equiv}CMe)Et$	2-Cl-4-MeO-Ph
174	Me	$CH(CH_2CH{=}CHMe)Et$	2-Cl-4-MeO-Ph
175	Me	$CH(Et)CH_2OH$	2-Cl-4,5-$(MeO)_2$-Ph
176	Me	$CH(Et)CH_2OMe$	2-Cl-4,5-$(MeO)_2$-Ph
177	Me	$CH(Et)CH_2CH_2OMe$	2-Cl-4,5-$(MeO)_2$-Ph
178	Me	3-pentyl	2-Cl-4,5-$(MeO)_2$-Ph
179	Me	2-pentyl	2-Cl-4,5-$(MeO)_2$-Ph
180	Me	2-butyl	2-Cl-4,5-$(MeO)_2$-Ph
181	Me	cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
182	Me	cyclopentyl	2-Cl-4,5-$(MeO)_2$-Ph
183	Me	CH(Me)cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
184	Me	CH(Me)cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
185	Me	CH(Et)cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph

186	Me	CH(Et)cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
187	Me	CH(Me)CH_2-cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
188	Me	CH(Me)CH_2-cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
189	Me	CH(Et)CH_2-cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
190	Me	CH(Et)CH_2-cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
191	Me	CH(CH_2OMe)cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
192	Me	CH(CH_2OMe)cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
193	Me	CH(CH_2OEt)cyclobutyl	2-Cl-4,5-$(MeO)_2$-Ph
194	Me	CH(CH_2OEt)cyclopropyl	2-Cl-4,5-$(MeO)_2$-Ph
195	Me	CH(cyclobutyl)$_2$	2-Cl-4,5-$(MeO)_2$-Ph
196	Me	CH(cyclopropyl)$_2$	2-Cl-4,5-$(MeO)_2$-Ph
197	Me	CH(Et)CH_2CONMe_2	2-Cl-4,5-$(MeO)_2$-Ph
198	Me	CH(Et)$CH_2CH_2NMe_2$	2-Cl-4,5-$(MeO)_2$-Ph
199	Me	CH(CH_2OMe)Me	2-Cl-4,5-$(MeO)_2$-Ph
200	Me	CH(CH_2OMe)Et	2-Cl-4,5-$(MeO)_2$-Ph
201	Me	CH(CH_2OMe)Pr	2-Cl-4,5-$(MeO)_2$-Ph
202	Me	CH(CH_2OEt)Me	2-Cl-4,5-$(MeO)_2$-Ph
203	Me	CH(CH_2OEt)Et	2-Cl-4,5-$(MeO)_2$-Ph
204	Me	CH(CH_2OEt)Pr	2-Cl-4,5-$(MeO)_2$-Ph
205	Me	CH($CH_2C\equiv CMe$)Et	2-Cl-4,5-$(MeO)_2$-Ph
206	Me	CH($CH_2CH=CHMe$)Et	2-Cl-4,5-$(MeO)_2$-Ph
207	Me	CH(Et)CH_2OH	2-Cl-4-MeO-5-F-Ph
208	Me	CH(Et)CH_2OMe	2-Cl-4-MeO-5-F-Ph
209	Me	CH(Et)CH_2CH_2OMe	2-Cl-4-MeO-5-F-Ph
210	Me	3-pentyl	2-Cl-4-MeO-5-F-Ph
211	Me	2-pentyl	2-Cl-4-MeO-5-F-Ph
212	Me	2-butyl	2-Cl-4-MeO-5-F-Ph
213	Me	cyclobutyl	2-Cl-4-MeO-5-F-Ph
214	Me	cyclopentyl	2-Cl-4-MeO-5-F-Ph
215	Me	CH(Me)cyclobutyl	2-Cl-4-MeO-5-F-Ph
216	Me	CH(Me)cyclopropyl	2-Cl-4-MeO-5-F-Ph
217	Me	CH(Et)cyclobutyl	2-Cl-4-MeO-5-F-Ph
218	Me	CH(Et)cyclopropyl	2-Cl-4-MeO-5-F-Ph
219	Me	CH(OEt)cyclobutyl	2-Cl-4-MeO-5-F-Ph
220	Me	CH(Me)CH_2-cyclobutyl	2-Cl-4-MeO-5-F-Ph

221	Me	CH(Me)CH_2-cyclopropyl	2-Cl-4-MeO-5-F-Ph
222	Me	CH(Et)CH_2-cyclobutyl	2-Cl-4-MeO-5-F-Ph
223	Me	CH(Et)CH_2-cyclopropyl	2-Cl-4-MeO-5-F-Ph
224	Me	CH(CH_2OMe)cyclobutyl	2-Cl-4-MeO-5-F-Ph
225	Me	CH(CH_2OMe)cyclopropyl	2-Cl-4-MeO-5-F-Ph
226	Me	CH(CH_2OEt)cyclobutyl	2-Cl-4-MeO-5-F-Ph
227	Me	CH(CH_2OEt)cyclopropyl	2-Cl-4-MeO-5-F-Ph
228	Me	CH(cyclobutyl)$_2$	2-Cl-4-MeO-5-F-Ph
229	Me	CH(cyclopropyl)$_2$	2-Cl-4-MeO-5-F-Ph
230	Me	CH(Et)CH_2CONMe$_2$	2-Cl-4-MeO-5-F-Ph
231	Me	CH(Et)CH_2CH_2NMe$_2$	2-Cl-4-MeO-5-F-Ph
232	Me	CH(CH_2OMe)Me	2-Cl-4-MeO-5-F-Ph
233	Me	CH(CH_2OMe)Et	2-Cl-4-MeO-5-F-Ph
234	Me	CH(CH_2OMe)Pr	2-Cl-4-MeO-5-F-Ph
234	Me	CH(CH_2OEt)Me	2-Cl-4-MeO-5-F-Ph
235	Me	CH(CH_2OEt)Et	2-Cl-4-MeO-5-F-Ph
236	Me	CH(CH_2OEt)Pr	2-Cl-4-MeO-5-F-Ph
237	Me	CH(CH_2C=CMe)Et	2-Cl-4-MeO-5-F-Ph
238	Me	CH(CH_2CH=CHMe)Et	2-Cl-4-MeO-5-F-Ph
239	Me	CH(Et)CH_2OH	2-Me-4-MeO-5-F-Ph
240	Me	CH(Et)CH_2OMe	2-Me-4-MeO-5-F-Ph
241	Me	CH(Et)CH_2CH_2OMe	2-Me-4-MeO-5-F-Ph
242	Me	3-pentyl	2-Me-4-MeO-5-F-Ph
243	Me	2-pentyl	2-Me-4-MeO-5-F-Ph
244	Me	2-butyl	2-Me-4-MeO-5-F-Ph
245	Me	cyclobutyl	2-Me-4-MeO-5-F-Ph
246	Me	cyclopentyl	2-Me-4-MeO-5-F-Ph
247	Me	CH(Me)cyclobutyl	2-Me-4-MeO-5-F-Ph
248	Me	CH(Me)cyclopropyl	2-Me-4-MeO-5-F-Ph
249	Me	CH(OMe)cyclopropyl	2-Me-4-MeO-5-F-Ph
250	Me	CH(Et)cyclobutyl	2-Me-4-MeO-5-F-Ph
251	Me	CH(Et)cyclopropyl	2-Me-4-MeO-5-F-Ph
252	Me	CH(Me)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
253	Me	CH(OMe)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
254	Me	CH(OH)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph

255	Me	CH(Me)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
256	Me	CH(Et)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
257	Me	CH(Et)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
258	Me	CH(OMe)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
259	Me	CH(OMe)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
260	Me	CH(OEt)CH_2-cyclobutyl	2-Me-4-MeO-5-F-Ph
261	Me	CH(OEt)CH_2-cyclopropyl	2-Me-4-MeO-5-F-Ph
262	Me	CH(CH_2OMe)cyclobutyl	2-Me-4-MeO-5-F-Ph
263	Me	CH(CH_2OMe)cyclopropyl	2-Me-4-MeO-5-F-Ph
264	Me	CH(CH_2OEt)cyclobutyl	2-Me-4-MeO-5-F-Ph
265	Me	CH(CH_2OEt)cyclopropyl	2-Me-4-MeO-5-F-Ph
266	Me	CH(cyclobutyl)$_2$	2-Me-4-MeO-5-F-Ph
267	Me	CH(cyclopropyl)$_2$	2-Me-4-MeO-5-F-Ph
268	Me	CH(Et)CH_2CONMe_2	2-Me-4-MeO-5-F-Ph
269	Me	CH(Et)$CH_2CH_2NMe_2$	2-Me-4-MeO-5-F-Ph
270	Me	CH(CH_2OMe)Me	2-Me-4-MeO-5-F-Ph
271	Me	CH(CH_2OMe)Et	2-Me-4-MeO-5-F-Ph
272	Me	CH(CH_2OMe)Pr	2-Me-4-MeO-5-F-Ph
273	Me	CH(CH_2OEt)Me	2-Me-4-MeO-5-F-Ph
274	Me	CH(CH_2OEt)Et	2-Me-4-MeO-5-F-Ph
275	Me	CH(CH_2OEt)Pr	2-Me-4-MeO-5-F-Ph
276	Me	CH($CH_2C{=}CMe$)Et	2-Me-4-MeO-5-F-Ph
277	Me	CH($CH_2C{=}CMe$)Et	2-Me-4-MeO-5-F-Ph
278	Me	CH(Et)CH_2OH	2,5-(Me)$_2$-4-MeO-Ph
279	Me	CH(Et)CH_2OMe	2,5-(Me)$_2$-4-MeO-Ph
280	Me	CH(Et)CH_2CH_2OMe	2,5-(Me)$_2$-4-MeO-Ph
281	Me	3-pentyl	2,5-(Me)$_2$-4-MeO-Ph
282	Me	2-butyl	2,5-(Me)$_2$-4-MeO-Ph
283	Me	cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph
284	Me	cyclopentyl	2,5-(Me)$_2$-4-MeO-Ph
285	Me	CH(Me)cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph
286	Me	CH(Me)cyclopropyl	2,5-(Me)$_2$-4-MeO-Ph
287	Me	CH(Et)cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph
288	Me	CH(Et)cyclopropyl	2,5-(Me)$_2$-4-MeO-Ph
289	Me	CH(Me)CH_2-cyclobutyl	2,5-(Me)$_2$-4-MeO-Ph

290	Me	CH(Me)CH_2-cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
291	Me	CH(Et)CH_2-cyclobutyl	2,5-$(Me)_2$-4-MeO-Ph
292	Me	CH(Et)CH_2-cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
293	Me	CH(CH_2OMe)cyclobutyl	2,5-$(Me)_2$-4-MeO-Ph
294	Me	CH(CH_2OMe)cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
295	Me	CH(CH_2OEt)cyclobutyl	2,5-$(Me)_2$-4-MeO-Ph
296	Me	CH(CH_2OEt)cyclopropyl	2,5-$(Me)_2$-4-MeO-Ph
297	Me	CH(cyclobutyl)$_2$	2,5-$(Me)_2$-4-MeO-Ph
298	Me	CH(cyclopropyl)$_2$	2,5-$(Me)_2$-4-MeO-Ph
299	Me	CH(Et)CH_2CONMe$_2$	2,5-$(Me)_2$-4-MeO-Ph
300	Me	CH(Et)CH_2CH_2NMe$_2$	2,5-$(Me)_2$-4-MeO-Ph
301	Me	CH(CH_2OMe)Me	2,5-$(Me)_2$-4-MeO-Ph
302	Me	CH(CH_2OMe)Et	2,5-$(Me)_2$-4-MeO-Ph
303	Me	CH(CH_2OMe)Pr	2,5-$(Me)_2$-4-MeO-Ph
304	Me	CH(CH_2OEt)Me	2,5-$(Me)_2$-4-MeO-Ph
305	Me	CH(CH_2OEt)Et	2,5-$(Me)_2$-4-MeO-Ph
306	Me	CH(CH_2OEt)Pr	2,5-$(Me)_2$-4-MeO-Ph
307	Me	CH(CH_2C≡CMe)Et	2,5-$(Me)_2$-4-MeO-Ph
308	Me	CH(CH_2CH=CHMe)Et	2,5-$(Me)_2$-4-MeO-Ph
309	Me	CH(Et)CH_2OH	2-Me-6-Me_2N-pyrid-3-yl
310	Me	CH(Et)CH_2OMe	2-Me-6-Me_2N-pyrid-3-yl
311	Me	CH(Et)CH_2CH_2OMe	2-Me-6-Me_2N-pyrid-3-yl
312	Me	3-pentyl	2-Me-6-Me_2N-pyrid-3-yl
313	Me	2-pentyl	2-Me-6-Me_2N-pyrid-3-yl
314	Me	2-butyl	2-Me-6-Me_2N-pyrid-3-yl
315	Me	cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
316	Me	cyclopentyl	2-Me-6-Me_2N-pyrid-3-yl
317	Me	CH(Me)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
318	Me	CH(Me)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
319	Me	CH(Et)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
320	Me	CH(Et)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
321	Me	CH(Me)CH_2-cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
322	Me	CH(Me)CH_2-cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
323	Me	CH(Et)CH_2-cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
324	Me	CH(Et)CH_2-cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl

325	Me	CH(CH_2OMe)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
326	Me	CH(CH_2OMe)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
327	Me	CH(CH_2OEt)cyclobutyl	2-Me-6-Me_2N-pyrid-3-yl
328	Me	CH(CH_2OEt)cyclopropyl	2-Me-6-Me_2N-pyrid-3-yl
329	Me	CH(cyclobutyl)$_2$	2-Me-6-Me_2N-pyrid-3-yl
330	Me	CH(cyclopropyl)$_2$	2-Me-6-Me_2N-pyrid-3-yl
331	Me	CH(Et)CH_2CONMe_2	2-Me-6-Me_2N-pyrid-3-yl
332	Me	CH(Et)$CH_2CH_2NMe_2$	2-Me-6-Me_2N-pyrid-3-yl
333	Me	CH(CH_2OMe)Me	2-Me-6-Me_2N-pyrid-3-yl
334	Me	CH(CH_2OMe)Et	2-Me-6-Me_2N-pyrid-3-yl
335	Me	CH(CH_2OMe)Pr	2-Me-6-Me_2N-pyrid-3-yl
336	Me	CH(CH_2OEt)Me	2-Me-6-Me_2N-pyrid-3-yl
337	Me	CH(CH_2OEt)Et	2-Me-6-Me_2N-pyrid-3-yl
338	Me	CH(CH_2OEt)Pr	2-Me-6-Me_2N-pyrid-3-yl
339	Me	CH($CH_2C{=}CMe$)Et	2-Me-6-Me_2N-pyrid-3-yl
340	Me	CH($CH_2CH{=}CHMe$)Et	2-Me-6-Me_2N-pyrid-3-yl
341	Me	CH(Et)CH_2OH	4-Me-2-Me_2N-pyrid-5-yl
342	Me	CH(Et)CH_2OMe	4-Me-2-Me_2N-pyrid-5-yl
343	Me	CH(Et)CH_2CH_2OMe	4-Me-2-Me_2N-pyrid-5-yl
344	Me	3-pentyl	4-Me-2-Me_2N-pyrid-5-yl
345	Me	2-pentyl	4-Me-2-Me_2N-pyrid-5-yl
346	Me	2-butyl	4-Me-2-Me_2N-pyrid-5-yl
347	Me	cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
348	Me	cyclopentyl	4-Me-2-Me_2N-pyrid-5-yl
349	Me	CH(Me)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
350	Me	CH(Me)cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
351	Me	CH(Et)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
352	Me	CH(Et)cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
353	Me	CH(Me)CH_2-cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
354	Me	CH(Me)CH_2-cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
355	Me	CH(Et)CH_2-cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
356	Me	CH(Et)CH_2-cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
357	Me	CH(CH_2OMe)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl
358	Me	CH(CH_2OMe)cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
359	Me	CH(CH_2OEt)cyclobutyl	4-Me-2-Me_2N-pyrid-5-yl

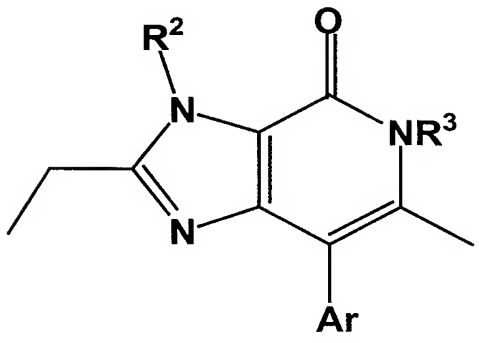
360	Me	$CH(CH_2OEt)$cyclopropyl	4-Me-2-Me_2N-pyrid-5-yl
361	Me	$CH(cyclobutyl)_2$	4-Me-2-Me_2N-pyrid-5-yl
362	Me	$CH(cyclopropyl)_2$	4-Me-2-Me_2N-pyrid-5-yl
363	Me	$CH(Et)CH_2CONMe_2$	4-Me-2-Me_2N-pyrid-5-yl
364	Me	$CH(Et)CH_2CH_2NMe_2$	4-Me-2-Me_2N-pyrid-5-yl
365	Me	$CH(CH_2OMe)Me$	4-Me-2-Me_2N-pyrid-5-yl
366	Me	$CH(CH_2OMe)Et$	4-Me-2-Me_2N-pyrid-5-yl
367	Me	$CH(CH_2OMe)Pr$	4-Me-2-Me_2N-pyrid-5-yl
368	Me	$CH(CH_2OEt)Me$	4-Me-2-Me_2N-pyrid-5-yl
369	Me	$CH(CH_2OEt)Et$	4-Me-2-Me_2N-pyrid-5-yl
370	Me	$CH(CH_2OEt)Pr$	4-Me-2-Me_2N-pyrid-5-yl
371	Me	$CH(CH_2C{\equiv}CMe)Et$	4-Me-2-Me_2N-pyrid-5-yl
372	Me	$CH(CH_2CH{=}CHMe)Et$	4-Me-2-Me_2N-pyrid-5-yl
373	Me	$CH(Et)CH_2OH$	2-Me-6-MeO-pyrid-3-yl
374	Me	$CH(Et)CH_2OMe$	2-Me-6-MeO-pyrid-3-yl
375	Me	$CH(Et)CH_2CH_2OMe$	2-Me-6-MeO-pyrid-3-yl
376	Me	3-pentyl	2-Me-6-MeO-pyrid-3-yl
377	Me	2-pentyl	2-Me-6-MeO-pyrid-3-yl
378	Me	2-butyl	2-Me-6-MeO-pyrid-3-yl
379	Me	cyclobutyl	2-Me-6-MeO-pyrid-3-yl
380	Me	cyclopentyl	2-Me-6-MeO-pyrid-3-yl
381	Me	CH(Me)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
382	Me	CH(Me)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
383	Me	CH(Et)cyclobutyl	2-Me-6-MeO-pyrid-3-yl
384	Me	CH(Et)cyclopropyl	2-Me-6-MeO-pyrid-3-yl
385	Me	$CH(Me)CH_2$-cyclobutyl	2-Me-6-MeO-pyrid-3-yl
386	Me	$CH(Me)CH_2$-cyclopropyl	2-Me-6-MeO-pyrid-3-yl
387	Me	$CH(Et)CH_2$-cyclobutyl	2-Me-6-MeO-pyrid-3-yl
388	Me	$CH(Et)CH_2$-cyclopropyl	2-Me-6-MeO-pyrid-3-yl
389	Me	$CH(CH_2OMe)$cyclobutyl	2-Me-6-MeO-pyrid-3-yl
390	Me	$CH(CH_2OMe)$cyclopropyl	2-Me-6-MeO-pyrid-3-yl
391	Me	$CH(CH_2OEt)$cyclobutyl	2-Me-6-MeO-pyrid-3-yl
392	Me	$CH(CH_2OEt)$cyclopropyl	2-Me-6-MeO-pyrid-3-yl
393	Me	$CH(cyclobutyl)_2$	2-Me-6-MeO-pyrid-3-yl
394	Me	$CH(cyclopropyl)_2$	2-Me-6-MeO-pyrid-3-yl

395	Me	CH(Et)CH_2CONMe_2	2-Me-6-MeO-pyrid-3-yl
396	Me	CH(Et)$CH_2CH_2NMe_2$	2-Me-6-MeO-pyrid-3-yl
397	Me	CH(CH_2OMe)Me	2-Me-6-MeO-pyrid-3-yl
398	Me	CH(CH_2OMe)Et	2-Me-6-MeO-pyrid-3-yl
399	Me	CH(CH_2OMe)Pr	2-Me-6-MeO-pyrid-3-yl
400	Me	CH(CH_2OEt)Me	2-Me-6-MeO-pyrid-3-yl
401	Me	CH(CH_2OEt)Et	2-Me-6-MeO-pyrid-3-yl
402	Me	CH(CH_2OEt)Pr	2-Me-6-MeO-pyrid-3-yl
403	Me	CH($CH_2C{\equiv}CMe$)Et	2-Me-6-MeO-pyrid-3-yl
404	Me	CH($CH_2CH{=}CHMe$)Et	2-Me-6-MeO-pyrid-3-yl
405	Me	CH(Et)CH_2OH	4-Me-2-MeO-pyrid-5-yl
406	Me	CH(Et)CH_2OMe	4-Me-2-MeO-pyrid-5-yl
407	Me	CH(Et)CH_2CH_2OMe	4-Me-2-MeO-pyrid-5-yl
408	Me	3-pentyl	4-Me-2-MeO-pyrid-5-yl
409	Me	2-pentyl	4-Me-2-MeO-pyrid-5-yl
410	Me	2-butyl	4-Me-2-MeO-pyrid-5-yl
411	Me	cyclobutyl	4-Me-2-MeO-pyrid-5-yl
412	Me	cyclopentyl	4-Me-2-MeO-pyrid-5-yl
413	Me	CH(Me)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
414	Me	CH(Me)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
415	Me	CH(Et)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
416	Me	CH(Et)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
417	Me	CH(Me)CH_2-cyclobutyl	4-Me-2-MeO-pyrid-5-yl
418	Me	CH(Me)CH_2-cyclopropyl	4-Me-2-MeO-pyrid-5-yl
419	Me	CH(Et)CH_2-cyclobutyl	4-Me-2-MeO-pyrid-5-yl
420	Me	CH(Et)CH_2-cyclopropyl	4-Me-2-MeO-pyrid-5-yl
421	Me	CH(CH_2OMe)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
422	Me	CH(CH_2OMe)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
423	Me	CH(CH_2OEt)cyclobutyl	4-Me-2-MeO-pyrid-5-yl
424	Me	CH(CH_2OEt)cyclopropyl	4-Me-2-MeO-pyrid-5-yl
425	Me	CH(cyclobutyl)$_2$	4-Me-2-MeO-pyrid-5-yl
426	Me	CH(cyclopropyl)$_2$	4-Me-2-MeO-pyrid-5-yl
427	Me	CH(Et)CH_2CONMe_2	4-Me-2-MeO-pyrid-5-yl
428	Me	CH(Et)$CH_2CH_2NMe_2$	4-Me-2-MeO-pyrid-5-yl
429	Me	CH(CH_2OMe)Me	4-Me-2-MeO-pyrid-5-yl

430	Me	CH(CH_2OMe)Et	4-Me-2-MeO-pyrid-5-yl	
431	Me	CH(CH_2OMe)Pr	4-Me-2-MeO-pyrid-5-yl	
432	Me	CH(CH_2OEt)Me	4-Me-2-MeO-pyrid-5-yl	
433	Me	CH(CH_2OEt)Et	4-Me-2-MeO-pyrid-5-yl	
434	Me	CH(CH_2OEt)Pr	4-Me-2-MeO-pyrid-5-yl	
435	Me	CH(CH_2C≡CMe)Et	4-Me-2-MeO-pyrid-5-yl	
436	Me	CH(CH_2CH=CHMe)Et	4-Me-2-MeO-pyrid-5-yl	
536	H	2-pentyl	2,4-Cl_2-5-F-Ph	159-160
537	Me	2-pentyl	2,4-Cl_2-5-F-Ph	120-121
538	Me	(R)-2-butyl	2,4-Cl_2-Ph	105-107
539	Me	(S)-2-butyl	2,4-Cl_2-Ph	oil
540	Me	2-pentyl	4-Br-2-Cl-Ph	97-98
541	Me	2-pentyl	Ph	oil
542	Me	2-pentyl	4-OMe-Ph	oil
543	Me	CH_2OCH_2Ph	2,4-Cl_2-Ph	oil
544	Me	H	2,4-Cl_2-Ph	234-235
545	H	CH_2OCH_2Ph	2,4-Cl_2-Ph	174-175
546	Me	n-butyl	2,4-Cl_2-Ph	oil
547	Me	CH_2CH_2OMe	2,4-Cl_2-Ph	oil
548	Me	3-heptyl	2,4-Cl_2-Ph	110-111
549	Me	(S)-2-pentyl	2,4-Cl_2-Ph	oil
550	Me	(R)-2-pentyl	2,4-Cl_2-Ph	oil
551	Me	CH(Et)CH_2C≡CH	2,4-Cl_2-Ph	oil
552	Me	2-hexyl	2,4-Cl_2-Ph	oil
553	Me	3-hexyl	2,4-Cl_2-Ph	135-136
554	Me	CH(Et)$CH_2CH_2CH=CH_2$	2,4-Cl_2-Ph	106-107
555	Me	CH($CH_2CH=CH_2$)$_2$	2,4-Cl_2-Ph	oil
556	Me	CH(Me)CH_2OCH_3	2,4-Cl_2-Ph	oil
557	Me	CH(n-C_3H_7)-cyclopropyl	2,4-Cl_2-Ph	139-140
558	Me	CH(Ph)-cyclopropyl	2,4-Cl_2-Ph	172-173
559	Me	CH(4-OMe-Ph)-cyclopropyl	2,4-Cl_2-Ph	oil
560	Me	CH(4-Me-Ph)-cyclopropyl	2,4-Cl_2-Ph	oil
561	Me	CH(4-F-Ph)-cyclopropyl	2,4-Cl_2-Ph	oil
562	Me	$CH_2CH(CH_3)_2$	2,4-Cl_2-Ph	oil
563	Me	$CH_2C(=CH_2)Me$	2,4-Cl_2-Ph	126-127

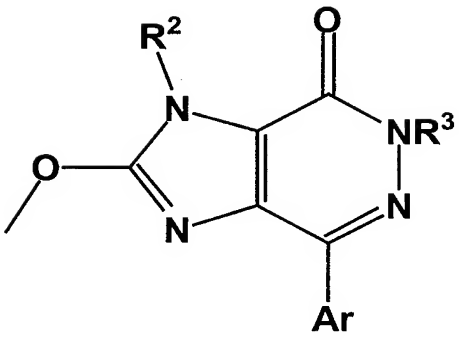
564	Me	$CH_2CH_2CH(CH_3)_2$	2,4-Cl_2-Ph	105-106
565	Me	$CH_2CH_2CH=CH_2$	2,4-Cl_2-Ph	oil
566	Me	$CH_2C\equiv CMe$	2,4-Cl_2-Ph	148-149
567	Me	(R)-$CH_2CH(Me)CH_2CH_3$	2,4-Cl_2-Ph	oil
568	Me	(S)-$CH_2CH(Me)CH_2CH_3$	2,4-Cl_2-Ph	oil
569	Me	$CH_2COCH_2CH_3$	2,4-Cl_2-Ph	104-105
570	Me	$CH_2CH(CH_2CH_3)_2$	2,4-Cl_2-Ph	oil
571	Me	n-pentyl	2,4-Cl_2-Ph	oil
572	Me	$CH_2(CH_2)_2CH=CH_2$	2,4-Cl_2-Ph	oil
573	Me	$CH_2CH=CHCH_2CH_3$	2,4-Cl_2-Ph	oil
574	Me	CH_2(2-Cl-Ph)	2,4-Cl_2-Ph	163-165
575	Me	CH_2(3-Cl-Ph)	2,4-Cl_2-Ph	82-84
576	Me	CH_2(4-Cl-Ph)	2,4-Cl_2-Ph	149-150
577	Me	CH_2(2,4-Cl_2-Ph)	2,4-Cl_2-Ph	85-87
578	Me	CH_2(2,4-F_2-Ph)	2,4-Cl_2-Ph	oil
579	Me	CH(Me)Ph	2,4-Cl_2-Ph	179-180
580	Me	CH_2CH_2Ph	2,4-Cl_2-Ph	oil
581	Me	CH_2-cyclobutyl	2,4-Cl_2-Ph	oil
582	Me	2-pentyl	2-4-CF_3-Ph	oil
583	Me	2-pentyl	2-Cl-4-F-Ph	oil
584	Me	2-pentyl	2,4-Cl_2-Ph	oil
585	Me	2-pentyl	2,6-$(OMe)_2$-pyrid-5-yl	oil

Table 2



Ex.	R_3	R_2	Ar	mp (°C)
437	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
438	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
439	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
440	Me	3-pentyl	2,4-Cl_2-Ph	
441	Me	2-pentyl	2,4-Cl_2-Ph	
442	Me	2-butyl	2,4-Cl_2-Ph	
443	Me	cyclobutyl	2,4-Cl_2-Ph	
444	Me	cyclopentyl	2,4-Cl_2-Ph	
445	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
446	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	
447	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
448	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	
449	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
450	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	
451	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph	
452	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph	
453	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph	
454	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph	
455	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph	
456	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph	
457	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph	
458	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph	
459	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph	
460	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph	
461	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Cl_2-Ph	
462	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph	
463	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph	
464	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph	
465	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph	
466	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph	
467	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph	
468	Me	CH($CH_2C{\equiv}CMe$)Et	2,4-Cl_2-Ph	
469	Me	CH($CH_2CH{=}CHMe$)Et	2,4-Cl_2-Ph	

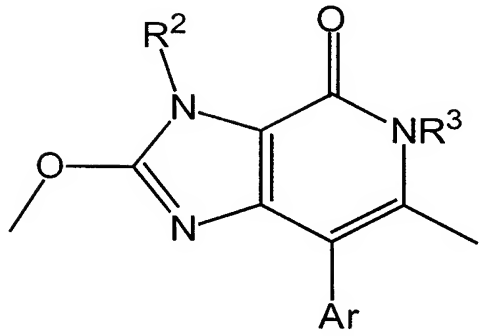
Table 3



Ex.	R_3	R_2	Ar	mp (°C)
470	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
471	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
472	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
473	Me	3-pentyl	2,4-Cl_2-Ph	
474	Me	2-pentyl	2,4-Cl_2-Ph	
475	Me	2-butyl	2,4-Cl_2-Ph	
476	Me	cyclobutyl	2,4-Cl_2-Ph	
477	Me	cyclopentyl	2,4-Cl_2-Ph	
478	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
479	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	
480	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
481	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	
482	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
483	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	
484	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph	
485	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph	
486	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph	
487	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph	
488	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph	
489	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph	
490	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph	
491	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph	
492	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph	

493	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph
494	Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Cl_2-Ph
495	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph
496	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph
497	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph
498	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph
499	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph
500	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph
501	Me	CH($CH_2C\equiv CMe$)Et	2,4-Cl_2-Ph
502	Me	CH($CH_2C\equiv CMe$)Et	2,4-Cl_2-Ph

Table 4



Ex.	R_3	R_2	Ar	mp (°C)
503	Me	CH(Et)CH_2OH	2,4-Cl_2-Ph	
504	Me	CH(Et)CH_2OMe	2,4-Cl_2-Ph	
505	Me	CH(Et)CH_2CH_2OMe	2,4-Cl_2-Ph	
506	Me	3-pentyl	2,4-Cl_2-Ph	
507	Me	2-pentyl	2,4-Cl_2-Ph	
508	Me	2-butyl	2,4-Cl_2-Ph	
509	Me	cyclobutyl	2,4-Cl_2-Ph	
510	Me	cyclopentyl	2,4-Cl_2-Ph	
511	Me	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
512	Me	CH(Me)cyclopropyl	2,4-Cl_2-Ph	
513	Me	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
514	Me	CH(Et)cyclopropyl	2,4-Cl_2-Ph	
515	Me	CH(Me)CH_2-cyclobutyl	2,4-Cl_2-Ph	
516	Me	CH(OH)CH_2-cyclobutyl	2,4-Cl_2-Ph	

517	Me	CH(Me)CH_2-cyclopropyl	2,4-Cl_2-Ph
518	Me	CH(Et)CH_2-cyclobutyl	2,4-Cl_2-Ph
519	Me	CH(Et)CH_2-cyclopropyl	2,4-Cl_2-Ph
520	Me	CH(CH_2OMe)cyclobutyl	2,4-Cl_2-Ph
521	Me	CH(CH_2OMe)cyclopropyl	2,4-Cl_2-Ph
522	Me	CH(CH_2OEt)cyclobutyl	2,4-Cl_2-Ph
523	Me	CH(CH_2OEt)cyclopropyl	2,4-Cl_2-Ph
524	Me	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph
525	Me	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph
526	Me	CH(Et)CH_2CONMe_2	2,4-Cl_2-Ph
527	Me	CH(Et)CH_2CH_2NMe_2	2,4-Cl_2-Ph
528	Me	CH(CH_2OMe)Me	2,4-Cl_2-Ph
529	Me	CH(CH_2OMe)Et	2,4-Cl_2-Ph
530	Me	CH(CH_2OMe)Pr	2,4-Cl_2-Ph
531	Me	CH(CH_2OEt)Me	2,4-Cl_2-Ph
532	Me	CH(CH_2OEt)Et	2,4-Cl_2-Ph
533	Me	CH(CH_2OEt)Pr	2,4-Cl_2-Ph
534	Me	CH($CH_2C{\equiv}CMe$)Et	2,4-Cl_2-Ph
535	Me	CH(CH_2CH=CHMe)Et	2,4-Cl_2-Ph

Examples shown above in Tables 1-4 wherein R^3 is H, C_2H_5, C_3H_7 or C_{1-6}alkylC_{3-6} cycloalkyl are also readily prepared according to the procedures disclosed herein.

CRF Receptor Binding Assay for the Evaluation of Biological Activity

Radioligand binding experiments

Compounds of the invention were tested for in vitro activity as CRF receptor antagonists. The tests described below demonstrated that the examples tested had K_is of 10,000 nM or less and are thus useful as CRF receptor antagonists. Preferred antagonists have or will have a K_i of 1,000 nM or less. Radioligand binding experiments were

performed with membranes from rat frontal cortex to determine binding affinities (K_i's) of test compounds for the rat CRH_1 receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in tissue buffer (containing 50 mM HEPES, 10 mM $MgCl_2$, 2 mM EGTA, and 1 µg/ml each of aprotonin, leupeptin, and pepstatin, pH 7.0 @ 23°C) using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 X g for 12 min and the resulting pellet was washed by two sequential re-suspension and centrifugation steps. The final pellet was suspended to tissue buffer to a working concentration of 0.1 mg/ml protein. Protein determinations were made using the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL) with bovine serum albumin as the standard.

All test compounds were prepared in assay buffer, which was identical to the tissue buffer except for the inclusion of 0.15 mM bacitracin and 0.1% w/v ovalbumin. Binding assay were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and initiated by the addition of 100 µl membrane homogenate (containing 40-60 µg protein) to 200 µl of assay buffer containing radioligands (150 pM, final concentration, [^{125}I] tyr° ovine CRH; New England Nuclear, MA) and competing test compounds. Specific binding was determined in the presence of 10 µM α-helical CRH. Competition experiments were conducted using 12 concentrations of ligand (ranging from 1 X 10^{-11} to 1 X 10^{-5} M). The reactions mixtures were incubated to equilibrium for 2 hr at 23°C and terminated by rapid filtration using a cell harvester (Inotech Biosystems Inc., Lansing MI) over GFF glass-fibers (pre-soaked in 0.3 % v/v polyethyleneimine). Filters were rapidly

washed 3X with 0.3 ml cold wash buffer (PBS, pH 7.0, containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

Binding affinities (K_i's) of ligands for the CRH_1 receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or Prism (GraphPad Prism, San Diego, CA). Data were best-fit by the one-site/state competition equation.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37°C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37°C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6m}) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 μl of [^{3}H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (1990).
Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of inbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally

administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related

sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

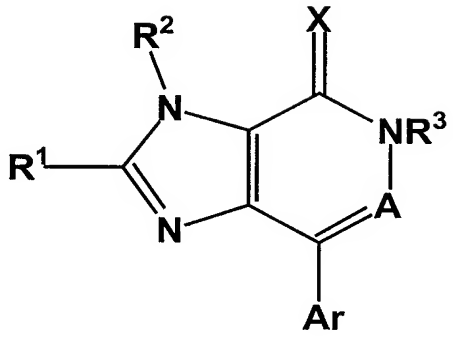
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (1):



(1)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

X is O or S;

A = N or CR^9;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached via an unsaturated carbon atom;

R^1 is independently selected at each occurrence from H, C_1-C_4†alkyl, C_2-C_4†alkenyl, C_2-C_4†alkynyl, halo, CN, C_1-C_4†haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl,

C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from:

-H, aryl, heteroaryl and heterocyclyl,

or

-C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_{1-6} alkyloxy-C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^3 is selected from:

-H, aryl, heteroaryl and heterocyclyl,

or

C_1-C_4†alkyl, C_3-C_6†alkenyl, C_3-C_6†alkynyl, C_3-C_6†cycloalkyl, C_4-C_{10} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12}†cycloalkylalkyl, NO_2, halo, CN, C_1-C_4†haloalkyl, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7,

OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12}†cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7 are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl optionally substituted by halogen, C_1-C_4 alkoxy or C_1-C_4 halo-alkoxy (1 to 4 halogens);

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally

substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2.

2. The compound according to claim 1 wherein Ar is phenyl or pyridyl, each optionally substituted with 1 to 4 R^4 substituents.

3. The compound according to claim 1 wherein Ar is phenyl wherein phenyl is optionally substituted with 1 to 3 R^4 substituents.

4. The compound according to claim 1 wherein R^2 is:

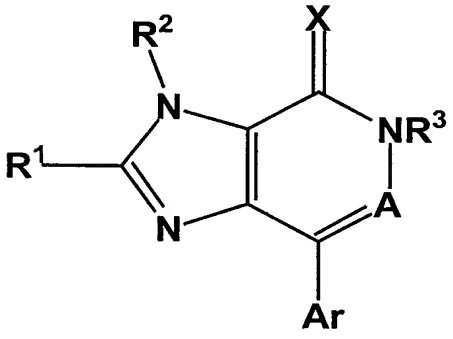
- C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH,

$S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl.

5. The compound according to claim 1 wherein R^1, R^2 and R^3 are independently selected from C_{1-6} alkyl or C_{1-6} alkyloxy.

6. A pharmaceutical composition comprising the compound of claim 1.

7. A method of antagonizing a CRF receptor in a mammal comprising contacting the receptor with a compound of the formula:



(1)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

X is O or S;

A = N or CR^9;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached via an unsaturated carbon atom;

R^1 is independently selected at each occurrence from H, C_1-C_4†alkyl, C_2-C_4†alkenyl, C_2-C_4†alkynyl, halo, CN, C_1-C_4†haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from:
-H, aryl, heteroaryl and heterocyclyl,
or
-C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^3 is selected from H, C_1-C_4†alkyl, C_3-C_6†alkenyl, C_3-C_6†alkynyl, C_3-C_6†cycloalkyl, C_4-C_{10} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each

occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12}†cycloalkylalkyl, NO_2, halo, CN, C_1-C_4†haloalkyl, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12}†cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^6COR^7, $NR^6CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7 are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl optionally substituted by halogen, C_1-C_4 alkoxy or C_1-C_4 halo-alkoxy (1 to 4 halogens);

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6†cycloalkyl, C_4-C_{12}†cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$,

COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2.

8. The method according to claim 7 wherein Ar is phenyl or pyridyl, each optionally substituted with 1 to 4 R^4 substituents.

9. The method according to claim 7 wherein Ar is phenyl wherein the phenyl is optionally substituted with 1 to 3 R^4 substituents.

10. The method according to claim 7 wherein R^2 is:

- C_1-C_{10}†alkyl, C_2-C_{10}†alkenyl, C_2-C_{10}†alkynyl, C_3-C_8†cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12}†cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6†alkyl, C_3-C_6†cycloalkyl, halo, C_1-C_4†haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl.

11. The method according to claim 7 wherein R^1, R^2 and R^3 are independently selected from C_{1-6} alkyl or C_{1-6} alkyloxy.

12. The method of claim 7 for treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF.

INTERNATIONAL SEARCH REPORT

Interna al application No.
PCT/US99/31325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 471/02, 487/02; A61K 31/4188; A61P 25/00
US CL : 544/236; 546/118; 514/248, 303

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/236; 546/118; 514/248, 303

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, E	WO 00/01697 A1 (DU PONT PHARMACEUTICALS COMPANY) 13 January 2000 (13.02.00), see entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
	19 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Brenda Coleman Telephone No. 703-308-1235

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Internationales Büro

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Veröffentlicht
Mit internationalem Recherchenbericht.

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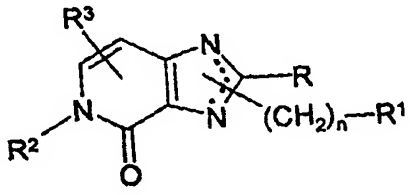
(54) Bezeichnung: IMIDAZO[4,5–C]–PYRIDIN–4–ON–DERIVATE



(I)

(57) Abstract

The invention relates to novel compounds of formula (I) wherein R, R^1, R^2, R^3 and n have the meaning given in Claim 1. Said compounds are inhibitors of the coagulation factor Xa and can be used for the prophylaxis and/or therapy of thrombo–embolic diseases.

(57) Zusammenfassung

Neue Verbindungen der Formel (I), worin R, R^1, R^2, R^3 und n die in Patentanspruch 1 angegebene Bedeutung haben, sind Inhibitoren des Koagulationsfaktors Xa und können zur Prophylaxe und/oder Therapie von thromboembolischen Erkrankungen eingesetzt werden.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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INTERNATIONAL SEARCH REPORT

Intel ɔnal Application No
PCT/EP 99/10236

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P9/10 //(C07D471/04,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 548 934 A (MITSUBISHI CHEM IND) 30 June 1993 (1993-06-30) page 46, line 57 -page 47, line 1; claim 1 ---	1,5
P,A	WO 99 27930 A (MERCK & CO INC (US)) 10 June 1999 (1999-06-10) claims 1,6 -----	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2000	30/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .onal Application No
PCT/EP 99/10236

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0548934 A	30-06-1993	CA 2085963 A	26-06-1993
		JP 6220044 A	09-08-1994
		US 5401756 A	28-03-1995
		US 5304556 A	19-04-1994
WO 9927930 A	10-06-1999	AU 1539599 A	16-06-1999
		US 6004976 A	21-12-1999

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 99/10236

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 C07D471/04 A61K31/437 A61P9/10 //(C07D471/04,235:00, 221:00)

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 C07D A61K A61P

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, WPI Data, CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 548 934 A (MITSUBISHI CHEM IND) 30. Juni 1993 (1993-06-30) Seite 46, Zeile 57 -Seite 47, Zeile 1; Anspruch 1	1,5
P,A	WO 99 27930 A (MERCK & CO INC (US)) 10. Juni 1999 (1999-06-10) Ansprüche 1,6	1,5

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
21. Juni 2000	30/06/2000

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

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INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Inter nales Aktenzeichen
PCT/EP 99/10236

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 0548934 A	30-06-1993	CA 2085963 A	26-06-1993
		JP 6220044 A	09-08-1994
		US 5401756 A	28-03-1995
		US 5304556 A	19-04-1994
WO 9927930 A	10-06-1999	AU 1539599 A	16-06-1999
		US 6004976 A	21-12-1999

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特許協力条約に基づいて公開された国際出願

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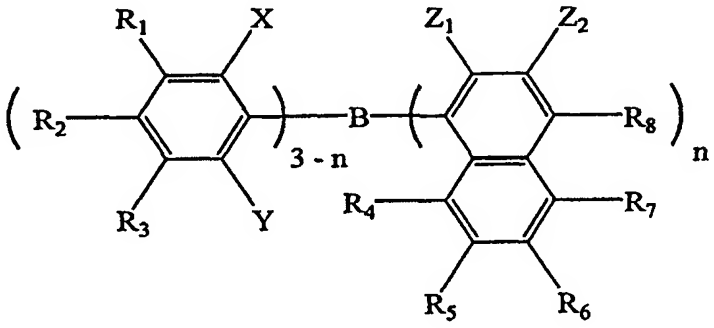
添付公開書類
国際調査報告書

(54)Title: **BORANE DERIVATIVES AND ORGANIC ELECTROLUMINESCENTS**

(54)発明の名称 ボラン誘導体および有機電界発光素子



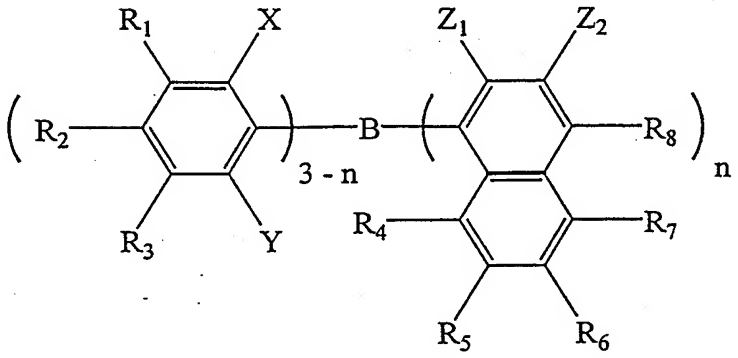
(1)

(57) Abstract

Borane derivatives represented by general formula (1) and organic electroluminescents, (wherein R_1 to R_8 and Z_2 are each independently hydrogen, saturated or unsaturated hydrocarbyl, an aromatic group, a heterocyclic group, substituted amino, substituted boryl, alkoxy or aryloxy; X, Y and Z_1 are each independently saturated or unsaturated hydrocarbyl, an aromatic group, a heterocyclic group, substituted amino, alkoxy or aryloxy; or alternatively Z_1 and Z_2 may be united to form a fused ring; and n is an integer of 1 to 3, with the provisos that Z_1s may be different from each other when n is 2 or above and that cases where n is 1; X, Y and R_2 are each methyl; and R_8 is hydrogen or substituted boryl and those where n is 3; and Z_1 is methyl are excepted). The borane derivatives are suitable for luminescent materials by virtue of their high luminous efficiencies in solid states, and useful for electrophotography and as photoelectronic functional materials including nonlinear optical materials and conductive materials, and the use of the derivatives brings about organic EL devices characterized by low power consumption and high efficiency.

(57)要約

本発明は、式（１）で表されるボラン誘導体および有機電界発光素子に関する。



（１）

（式中、R_1～R_8およびZ_2は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、Ｘ、ＹおよびZ_1は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、Z_1とZ_2の置換基は相互に結合して縮合環を形成してもよく、ｎは１～３の整数を示し、ｎが２以上の場合、Z_1は異なってもよい。但し、ｎが１、Ｘ、ＹおよびR_2がメチル基であって、R_8が水素原子または置換ボリル基の場合、およびｎが３でZ_1がメチル基の場合を含まない。）

本発明のボラン誘導体は、固体状態での発光効率が高いので発光材料として好適であり、電子写真、非線形光学材料および導電性材料などの光電子機能材料としても有用である。このボラン誘導体を用いることによって、低消費電力で高効率の有機ＥＬ素子を提供することができる。

明　細　書

ボラン誘導体および有機電界発光素子

技術分野

本発明は、新規なボラン誘導体、ボラン誘導体を用いた各種材料および有機電界発光素子（以下、有機ＥＬ素子という）に関する。さらに詳しくは、新規な構造を有するボラン誘導体、電子機能性材料、光機能性材料などの用途に有用な構造を有するボラン誘導体を用いた各種材料および有機ＥＬ素子に関する。

背景技術

π電子系有機化合物を光機能材料や電子機能材料に応用しようとする試みが多くの研究機関で行われており、その内容は多種多彩である。

中でも、ボロン原子を分子内に含むボラン化合物は、ボロン原子の空のｐ軌道の存在によって、特異な光学、電子物性が発現されると予想されている。しかしながら、一般にボラン化合物は、空気や水に対して不安定であるという欠点を有しているため、材料としての使用には不向きであった。

この様な問題に対して、最近、ボラン化合物を嵩高い構造にすると、つまりボロン原子のまわりに嵩高い置換基を導入してボロン原子を覆い、ボロン原子を外に出さないようにすると、空気や水に対して安定になるという報告がされたこともあり、そのような構造を有するボラン化合物が非線形光学材料や有機ＥＬ素子の材料等に応用できる可能性が広がった。

空気中で安定であるボラン化合物の例が、J. Chem. Soc. Chem. Commun., 1998, 963.（以下、文献１という）、J. Am. Chem. Soc., 120, 10776(1998)（以下、文献２という）およびJ. Am. Chem. Soc., 120, 5112(1998)（以下、文献３という）に報告され、ボラン化合物の非線形光学材料への応用例が、Appl. Organomet. Chem., 10, 305(1996)（以下、文献４という）に報告され、ボラン化合物の有機ＥＬ素子への

応用例が、J. Am. Chem. Soc., 120, 9714(1998)（以下、文献５という）に報告されている。

しかし、文献２および文献３には、蛍光の極大波長が記載されているが、溶液状態での発光特性に限定されており、実際に使用する固体状態での発光特性に関する記載が全くない。また、その構造もポリマーに限定されており、低分子化合物に関しては何も記載されていない。

文献４にも、溶液状態での蛍光物性は記載されているが、固体状態での発光性に関する記載が無く、また、発光材料への応用に関しても記載がない。

この様に、嵩高い構造を有するボラン化合物を実質的な用途に用いるには、充分な研究が行われていると言えないのが現状である。特に、有機ＥＬ素子への材料に応用することが熱望されており、この種の研究がさかんに行われているが、いまだ満足のゆく結果は得られていなかった。

有機ＥＬ素子は、基本的には２つの電極に電荷輸送材料または／および発光材料となる有機化合物を挟んだ構造からなる。低消費電力で高効率な有機ＥＬ素子であることが望ましく、そのためには発光効率の高い発光材料となる有機化合物を用いる必要がある。

ところが、文献５には、５，５’－ビス（ジメシチルボリル）－２，２’－（ビチオフェン）や５，５”－ビス（ジメシチルボリル）－２，２’：５’，２”－（ターチオフェン）のようなボラン化合物を有機ＥＬ素子の電子輸送材料（電荷輸送材料）に用いることが記載されているものの、該ボラン化合物の発光特性および該ボラン化合物の発光材料としての適性に関しては全く触れられていない。わずかに、ボラン化合物を用いない素子に比べ該ボラン化合物を用いた素子は、同輝度における電流密度が低いので、発光効率が向上していることを意味するという報告がなされているに過ぎない。

また、特開平７－１０２２５１号公報においても、ホウ素化合物を有機ＥＬ素子に利用した例が示されている。しかし、ここで用いられているホウ素化合物は、駆動電圧が高く、発光輝度も低いものであった。

この様に、ボラン化合物の発光特性に関する文献等が少ないため、有機ＥＬ素子の材料としてこれまでに知られているボラン化合物では、低消費電力で高効率

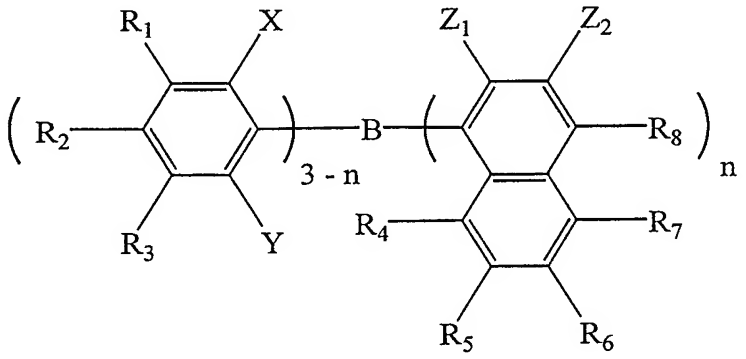
な有機ＥＬ素子を得ることができなかった。そのため、有機ＥＬ素子の材料として有効に働くボラン化合物の構造特定が望まれていた。

発明の開示

本発明者等は、新規なボラン誘導体、ボラン誘導体を用いた各種材料および有機ＥＬ素子を提供するという課題を解決すべく鋭意検討を進めた結果、特定構造を有するボラン誘導体および特定構造を有するボラン誘導体を材料に用いること、特に有機ＥＬ素子に用いることにより、上記課題を解決し得ることを知り本発明を完成した。

以下、本発明につき詳細に説明する。

本発明のボラン誘導体は、下記の式（１）で表される新規な化合物である。本発明のボラン誘導体は、発光材料および電荷輸送材料ばかりでなく、ボラン原子に由来する電子的性質を利用して、電子機能性材料および光機能性材料などへの広範な応用が期待できるものである。



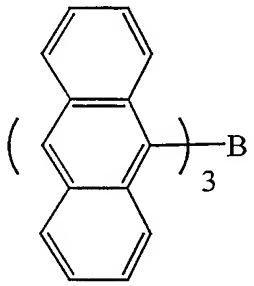
(1)

（式中、R_1～R_8およびZ_2は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、Ｘ、ＹおよびZ_1は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、Z_1とZ_2の置換基は相互に結合して縮合環を形成してもよく、ｎは１～３の整数を示し、ｎが２以上の場合、Z_1は異なってもよい。但し、ｎが１、Ｘ、ＹおよびR_2がメチル基であって、R_8

が水素原子または置換ボリル基の場合、およびｎが３でＺ$_1$がメチル基の場合を含まない。）

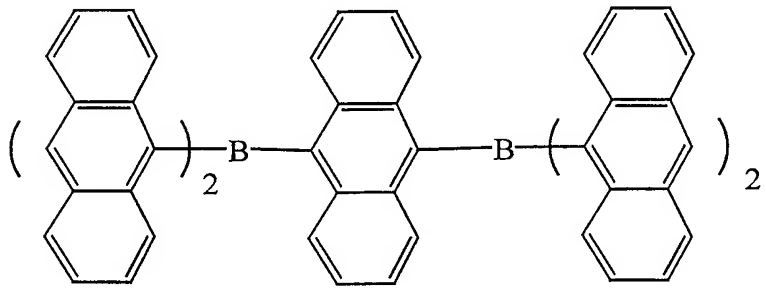
そして、この式（１）で表されるボラン誘導体の中でも、ボロン原子に対して少なくとも１個の置換もしくは無置換の９－アンスリル基が結合しているものが好ましい。

本発明のボラン誘導体の具体的例として、下記の式（３）～（９）で表される化合物を挙げることができる。



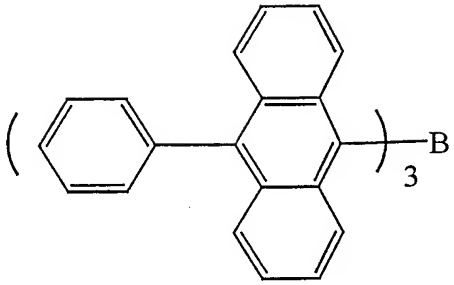
（３）

式（３）の化合物は、上記の式（１）において、ｎが３、Ｒ$_4$～Ｒ$_8$が水素原子、Ｚ$_1$とＺ$_2$とがベンゾ縮合したボラン誘導体である。



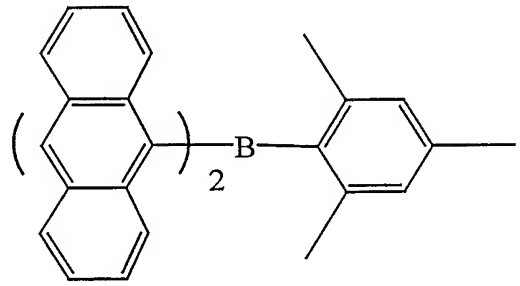
（４）

式（４）の化合物は、上記の式（１）において、ｎが３、Ｒ$_4$～Ｒ$_7$が水素原子、Ｒ$_8$の１つがジアンスリルボリル基、Ｒ$_8$の残り２つが水素原子、Ｚ$_1$とＺ$_2$とがベンゾ縮合したボラン誘導体である。



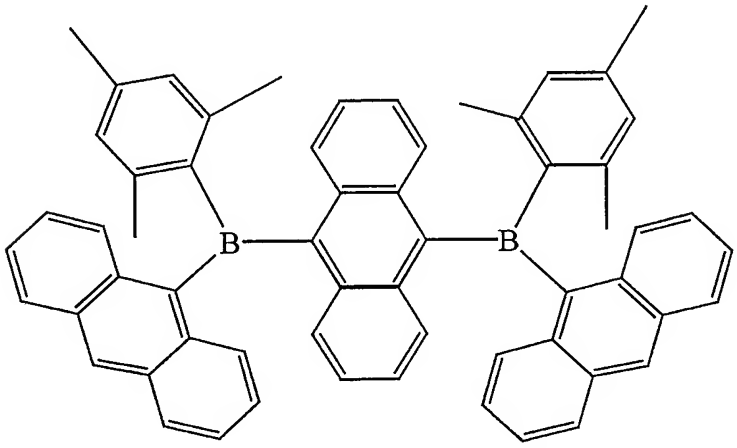
(5)

式（５）の化合物は、上記の式（１）において、R_4～R_7が水素原子、R_8がフェニル基、ｎが３、Z_1とZ_2とがベンゾ縮合したボラン誘導体である。



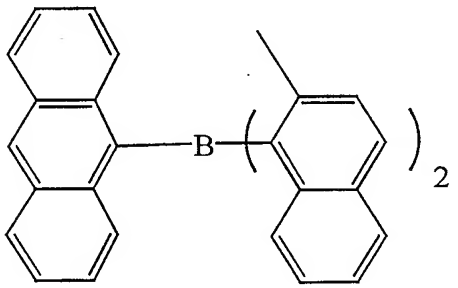
(6)

式（６）の化合物は、上記の式（１）において、ｎが２、R_1およびR_3～R_8が水素原子、R_2、ＸおよびＹがメチル基、Z_1とZ_2とがベンゾ縮合したボラン誘導体である。



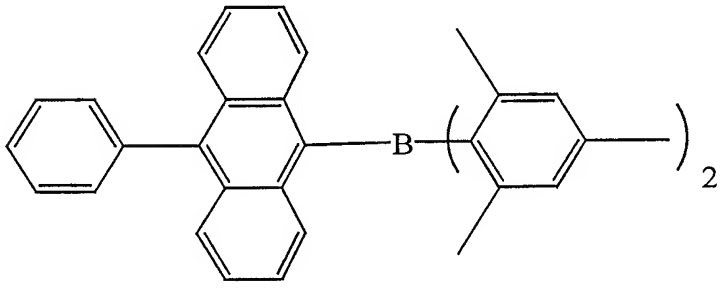
(7)

式（７）の化合物は、上記の式（１）において、ｎが２、R_1 およびR_3 ～R_7 が水素原子、R_2 、ＸおよびＹがメチル基、R_8 の１つがアンスリルメシチルボリル基、R_8 の残り１つが水素原子、Z_1 とZ_2 とがベンゾ縮合したボラン誘導体である。



(8)

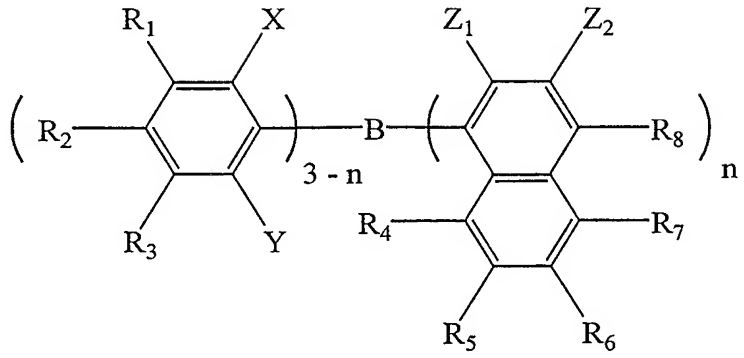
式（８）の化合物は、上記の式（１）において、ｎが３、R_4 ～R_8 が水素原子、Z_1 とZ_2 が１カ所でベンゾ縮合し、縮合していない残り２つのZ_1 がメチル基、縮合していない残り２つのZ_2 が水素原子のボラン誘導体である。



(9)

式（９）の化合物は、上記の式（１）において、ｎが１、R_1 およびR_3～R_7 が水素原子、R_2 、ＸおよびＹがメチル基、R_8 がフェニル基、Z_1 とZ_2 とがベンゾ縮合したボラン誘導体である。

本発明の各種材料、すなわち発光材料、電荷輸送材料および有機ＥＬ素子関連材料（発光層、電荷輸送層）に用いられるボラン誘導体は、下記の式（２）で表される。



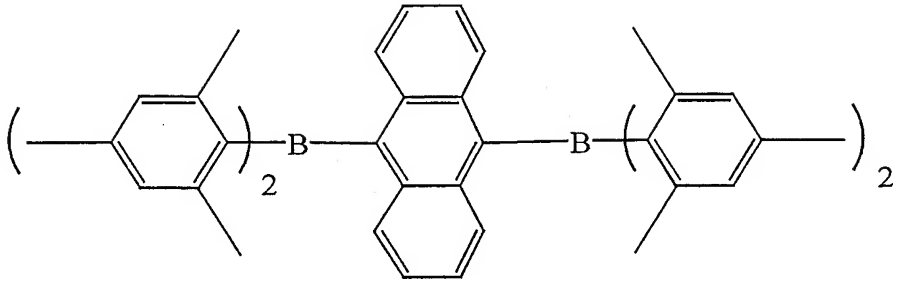
(2)

（式中、R_1～R_8およびZ_2は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、X、YおよびZ_1は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、Z_1とZ_2の置換基は相互に結合して縮合環を形成してもよく、nは1～3の整数を示し、nが2以上の場合、Z_1は異なってもよい。）

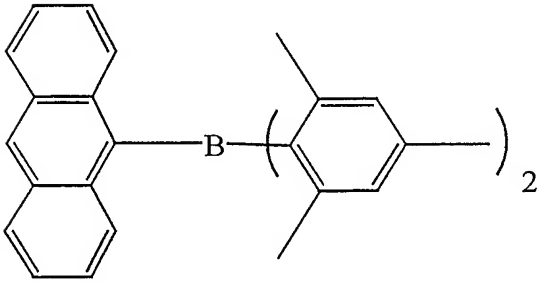
該ボラン誘導体は、空気中においても安定で、材料としての充分な耐久性および性能を持たせるため、嵩高い構造であることが好ましく、アントラセン環および／またはナフタレン環を有していることが望ましい。

従って、本発明の発光材料、電荷輸送材料および有機ＥＬ素子には、上記の式（２）で表されるボラン誘導体の中でも、ボロン原子に対して少なくとも１個の置換もしくは無置換の９－アンスリル基が結合しているものが好ましい。

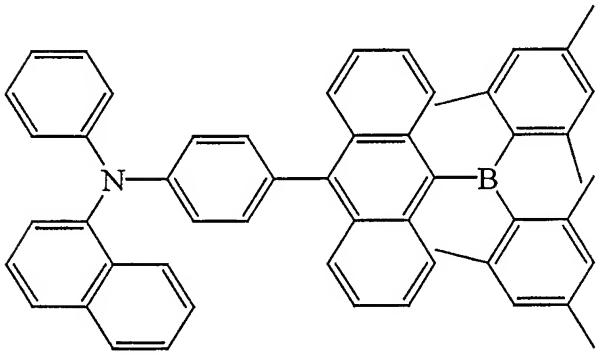
このようなボラン誘導体の具体例として、前記の式（３）～（９）で表される化合物および下記の式（１０）～（１４）で表される化合物などを挙げることができる。



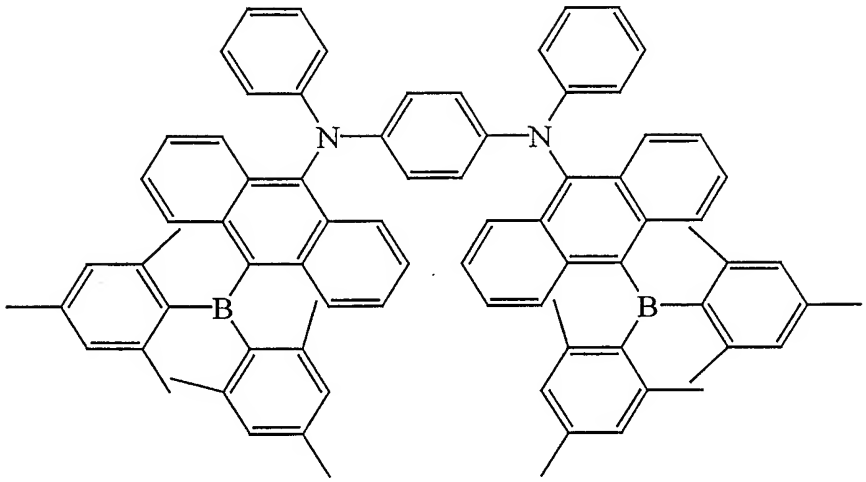
(10)



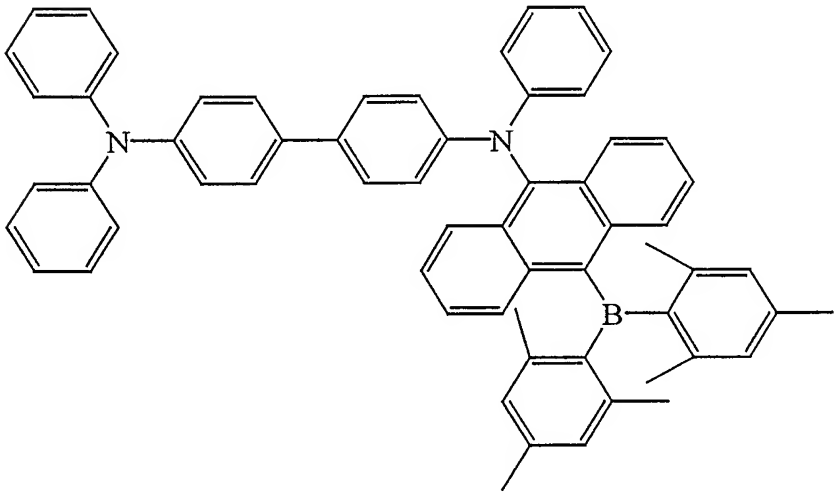
(11)



(12)



(13)

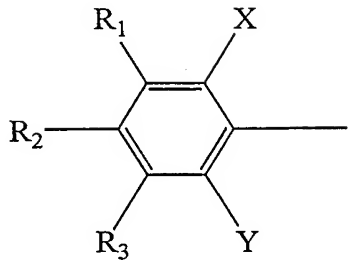


(14)

本発明のボラン誘導体および本発明の各種材料に用いられるボラン誘導体（以下、便宜的に本発明のボラン誘導体と略す）は、以下に示す製造法に代表される公知の手法により合成することができる。すなわち、一般式（１５）で表される化合物に塩基を反応させ、続いてボラン化合物を反応させることにより合成できる。

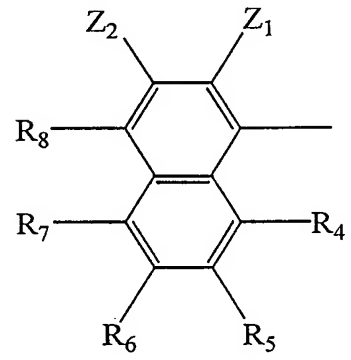
ＡｒＷ （１５）

（式中、Ａｒは下記の式（１６）または式（１７）を示し、Ｗはハロゲン原子を示す。）



(16)

(式中、R_1～R_3は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、XおよびYは、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示す。)



(17)

(式中、R_4～R_8およびZ_2は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、Z_1は飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、Z_1とZ_2の置換基は相互に結合して縮合環を形成してもよい。)

この製造法において用いられる塩基としては、例えば、n-ブチルリチウム、tert-ブチルリチウム、フェニルリチウムなどの有機リチウム試薬、マグネシウム、マグネシウムブロマイドなどのマグネシウム試薬等が挙げられる。また、用いられる溶媒としては、これらの塩基に不活性なものなら特に制限はなく、通常、

ジエチルエーテルあるいはテトラヒドロフラン（以下、ＴＨＦという）のようなエーテル系もしくはベンゼン、トルエンなどの芳香族系の溶媒が用いられる。さらに、用いられるボラン化合物としては、トリクロロボラン、トリフルオロボランまたはそれらの錯体などのハロゲン化ボラン類、トリメトキシボランまたはトリイソプロポキシボランなどのアルコキシボラン類などが挙げられる。

これらの反応は、不活性ガス中で行うことが好ましく、窒素およびアルゴンガスなどが使われる。反応温度は、特に制限はないが、通常、－７８℃～１２０℃程度が好ましい。これらの反応には、特に反応時間に制限はなく、反応が十分に進行している時点で反応を止めればよい。ＮＭＲあるいはクロマトグラフィー等の一般的な分析手段により反応を追跡し、最適の時点で反応の終点を決定すればよい。

また、得られた化合物に対して、置換反応を行うことによっても本発明のボラン誘導体が得られる。

置換反応によって付加する置換基としては、メチル基、エチル基、ノルマルプロピル基、イソプロピル基、シクロペンチル基、およびtert-ブチル基などのアルキル基、ビニル基、アリル基、ブテニル基およびスチリル基などのアルケニル基、メトキシ基、エトキシ基、プロポキシ基、フェニルオキシ基などのアルコキシ基もしくはアリールオキシ基、ジメチルアミノ基、ジフェニルアミノ基などのアミノ基、トリメチルシリル基、ジメチル-tert-ブチルシリル基、トリメトキシシリル基およびトリフェニルシリル基などのシリル基、ジアンスリルボリル基、ジメシチルボリル基などのボリル基、フェニル基、ナフチル基、アンスリル基、ビフェニル基、トルイル基、ピレニル基、ペリレニル基、アニシル基、ターフェニル基およびフェナンスレニル基などのアリール基、ヒドロフリル基、ヒドロピレニル基、ジオキサニル基、チエニル基、フリル基、オキサゾリル基、オキサジアゾリル基、チアゾリル基、チアジアゾリル基、アクリジニル基、キノリル基、キノキサロイル基、フェナンスロリル基、ベンゾチエニル基、ベンゾチアゾリル基、インドリル基、シラシクロペンタジエニル基およびピリジル基などのヘテロ環などが挙げられる。

更に、これらの置換基がお互いに任意の場所で結合して環を形成しても良い。

本発明の有機ＥＬ素子は、基本的には一対の電極（陽極と陰極）間に、前記の式（２）で表されるボラン誘導体を主成分とするボラン誘導体層を挟持した構造を有するものである。

該ボラン誘導体は、発光材料としても電荷輸送材料としても使用可能であるため、発光層および電荷輸送層（正孔注入層、正孔輸送層、電子注入層および電子輸送層）の材料に好適であり、得られた該ボラン誘導体層は、発光層および電荷輸送層として有効に働く。

また、該ボラン誘導体層には、該ボラン誘導体以外の正孔注入材料、正孔輸送材料、発光材料、電子注入材料あるいは電子輸送材料などが添加されていても良い。

有機ＥＬ素子においては、多くの場合、電荷輸送材料となる電子供与性化合物と電子受容性化合物とが用いられており、これらの混合物を添加したり、これらを積層したりして使用されているが、これらは好ましくない電荷移動錯体又はエキサイプレックスを形成することも知られている。しかし、本発明で用いられるボラン誘導体は、ボロン原子に結合している嵩高い基が、ボロン原子を中心としてプロペラ状に配置されているため、電荷移動錯体又はエキサイプレックスを形成しにくい構造となっている。従って、該ボラン誘導体を電子供与性化合物または電子受容性化合物として有機ＥＬ素子の材料に使用すると、高効率な素子が得られやすい利点を有している。

本発明の有機ＥＬ素子には、電極間に該ボラン誘導体層の他に、正孔注入層、正孔輸送層、発光層、電子注入層、電子輸送層および界面層などを任意に設けても何等差し支えない。

本発明の有機ＥＬ素子の具体的な構成としては、

構成（１）陽極／ボラン誘導体層／陰極

構成（２）陽極／正孔注入層／ボラン誘導体層／陰極

構成（３）陽極／ボラン誘導体層／電子注入層／陰極

構成（４）陽極／正孔注入層／ボラン誘導体層／電子注入層／陰極

構成（５）陽極／正孔注入層／ボラン誘導体層／電子輸送層／界面層／陰極

構成（６）陽極／正孔注入層／正孔輸送層／ボラン誘導体層／電子注入層／陰極

構成（７）陽極／正孔注入層／正孔輸送層／ボラン誘導体層／電子注入層／界面層／陰極

などの積層構造を挙げることができる。

この場合、正孔注入層、電子注入層、正孔輸送層、電子輸送層および界面層は、必ずしも必要ではないが、これらの層を設けることにより、発光効率を向上させることができる。特に、正孔注入層及び正孔輸送層の導入は、発光効率を大幅に向上させる。

本発明の有機ＥＬ素子は、基板に支持されていることが好ましい。

基板としては、機械的強度、熱安定性および透明性を有するものであればよく、ガラス、透明プラスチックフィルムなどを用いることができる。

本発明の有機ＥＬ素子の陽極に用いられる陽極物質としては、４ｅＶより大きな仕事関数を有する金属、合金、電気伝導性化合物及びこれらの混合物を用いることができる。具体例として、Ａｕなどの金属、ＣｕＩ、インジウムチンオキサイド（以下、ＩＴＯという）、SnO_2、ＺｎＯなどの導電性透明材料が挙げられる。

また、本発明の有機ＥＬ素子の陰極に用いられる陰極物質としては、４ｅＶより小さな仕事関数の金属、合金、電気伝導性化合物、およびこれらの混合物を使用できる。具体例としては、カルシウム、マグネシウム、リチウム、アルミニウム、マグネシウム合金、リチウム合金、アルミニウム合金等があり、混合物としてはアルミニウム／リチウム、マグネシウム／銀、マグネシウム／インジウムなどが挙げられる。

本発明では、有機ＥＬ素子の発光を効率よく取り出すために、電極の少なくとも一方は光透過率が１０％以上とすることが望ましい。電極としてのシート抵抗は数百Ω／ｍｍ以下とするのが好ましい。なお、膜厚は電極材料の性質にもよるが、通常１０ｎｍ～１μｍ、好ましくは１０～４００ｎｍの範囲で選定される。このような電極は、上述の電極物質（陽極物質と陰極物質）を使用して蒸着やスパッタリングなどの方法により薄膜を形成させることにより作製することができる。

本発明の有機ＥＬ素子の必須構成層である発光層には、前記の式（２）で表さ

れるボラン誘導体が用いられていることが望ましいが、該ボラン誘導体以外の発光材料が用いられても良い。また、式（２）で表されるボラン誘導体と該ボラン誘導体以外の発光材料との混合物を用い、該ボラン誘導体とは異なる波長の光を発生させたり、さらに発光効率を向上させることもできる。なお、式（２）で表されるボラン誘導体を２種以上組み合わせて用いることにも、何ら問題はない。

この様な式（２）で表されるボラン誘導体以外の発光材料には、高分子学会編高分子機能材料シリーズ”光機能材料”、共立出版(1991)、P236 に記載されているような昼光蛍光材料、蛍光増白剤、レーザー色素、有機シンチレータ、各種の蛍光分析試薬などの公知物質を挙げることができる。

具体的には、アントラセン、フェナントレン、ピレン、クリセン、ペリレン、コロネン、ルブレン、キナクリドンなどの多環縮合化合物、クオーターフェニルなどのオリゴフェニレン系化合物、1,4-ビス(2-メチルスチリル)ベンゼン、1,4-ビス(4-メチルスチリル)ベンゼン、1,4-ビス(4-メチル-5-フェニル-2-オキザゾリル)ベンゼン、1,4-ビス(5-フェニル-2-オキサゾリル)ベンゼン、2,5-ビス(5-タシャリー-ブチル-2-ベンズオキサゾリル)チオフェン、1,4-ジフェニル-1,3-ブタジエン、1,6-ジフェニル-1,3,5-ヘキサトリエン、1,1,4,4-テトラフェニル-1,3-ブタジエンなどの液体シンチレーション用シンチレータ、特開昭６３－２６４６９２号公報記載のオキシン誘導体の金属錯体、クマリン染料、ジシアノメチレンピラン染料、ジシアノメチレンチオピラン染料、ポリメチン染料、オキソベンズアントラセン染料、キサンテン染料、カルボスチリル染料およびペリレン染料、独国特許２５３４７１３号公報に記載のオキサジン系化合物、第40回応用物理学関係連合講演会講演予稿集、1146(1993)に記載のスチルベン誘導体、特開平７－２７８５３７号公報記載のスピロ化合物および特開平４－３６３８９１号公報記載のオキサジアゾール系化合物などが好ましい。

本発明の有機ＥＬ素子の選択的構成層である正孔注入層は、正孔注入材料を用いて得ることができるが、この際、一種以上の正孔注入材料を用いて１層の正孔注入層を得ても良く、異なる数種の正孔注入材料を用いて複数の正孔注入層を得ても良い。

また、本発明の有機ＥＬ素子の選択的構成層である正孔輸送層は、正孔輸送材

料を用いて得ることができるが、この際、一種以上の正孔輸送材料を用いて１層の正孔輸送層を得ても良く、異なる数種の正孔輸送材料を用いて複数の正孔輸送層を得ても良い。

該正孔注入材料および該正孔輸送材料には、前記の式（２）で表されるボラン誘導体を用いることができるが、光導電材料において、正孔の電荷輸送材料として従来から慣用されているものや、有機ＥＬ素子の正孔注入層および正孔輸送層に使用され得る公知物質の中から任意のものを選択して用いることもできる。

この様な公知物質としては、例えば、カルバゾール誘導体（N-フェニルカルバゾール、ポリビニルカルバゾールなど）、トリアリールアミン誘導体（ＴＰＤ、芳香族第３級アミンを主鎖あるいは側鎖に持つポリマー、1,1-ビス(4-ジ-p-トリルアミノフェニル)シクロヘキサン、N,N'-ジフェニル-N,N'-ジナフチル-4,4'-ジアミノビフェニル（以下、ＮＰＤと略記する）、4,4',4''-トリス{N-(3-メチルフェニル)-N-フェニルアミノ}トリフェニルアミン、ジャーナル・オブ・ザ・ケミカル・ソサイエティー・ケミカル・コミュニケーション第2175ページ1996年に記載されている化合物、特開昭５７－１４４５５８号公報、特開昭６１－６２０３８号公報、特開昭６１－１２４９４９号公報、特開昭６１－１３４３５４号公報、特開昭６１－１３４３５５号公報、特開昭６１－１１２１６４号公報、特開平４－３０８６８８号公報、特開平６－３１２９７９号公報、特開平６－２６７６５８号公報、特開平７－９０２５６号公報、特開平７－９７３５５号公報、特開平６－１９７２号公報、特開平７－１２６２２６号公報、特開平７－１２６６１５号公報、特開平７－３３１２３８号公報、特開平８－１００１７２号公報および特開平８－４８６５６号公報に記載されている化合物、アドバンスド・マテリアル第6巻第677ページ1994年に記載されているスターバーストアミン誘導体など）、スチルベン誘導体（日本化学会第72春季年会講演予稿集(II)、1392ページ、2PB098に記載のものなど）、フタロシアニン誘導体（無金属、銅フタロシアニンなど）、ポリシランなどが挙げられる。

本発明の有機ＥＬ素子の選択的構成層である電子注入層は、電子注入材料を用いて得ることができるが、この際、一種以上の電子注入材料を用いて１層の電子注入層を得ても良く、異なる数種の電子注入材料を用いて複数の電子注入層を得

ても良い。

また、本発明の有機ＥＬ素子の選択的構成層である電子輸送層は、電子輸送材料を用いて得ることができるが、この際、一種以上の電子輸送材料を用いて１層の電子輸送層を得ても良く、異なる数種の電子輸送材料を用いて複数の電子輸送層を得ても良い。

該電子注入材料および該電子輸送材料には、前記の式（２）で表されるボラン誘導体を用いることが望ましいが、光導電材料において、電子伝達化合物として従来から慣用されているもの、有機ＥＬ素子の電子注入層および電子輸送層に使用され得る公知物質の中から任意のものを選択して用いることができる。

この様な公知物質としては、例えば、ジフェニルキノン誘導体（電子写真学会誌、30,3(1991)などに記載のもの）、ペリレン誘導体(J.Apply.Phys.,27,269(1988)などに記載のもの)や、オキサジアゾール誘導体（前記文献、Jpn.J.Appl.Phys.,27,L713(1988)、アプライド・フィジックス・レター(Appl.Phys.Lett.),55,1489(1989)などに記載のもの）、チオフェン誘導体（特開平４－２１２２８６号公報などに記載のもの）、トリアゾール誘導体（Jpn.J.Appl.Phys.,32,L917(1993)などに記載のもの）、チアジアゾール誘導体（第43回高分子学会予稿集、(III)P1a007などに記載のもの）、オキシン誘導体の金属錯体（電子情報通信学会技術研究報告、92(311),43(1992)などに記載のもの）、キノキサリン誘導体のポリマー（Jpn.J.Appl.Phys.,33,L250(1994)などに記載のもの）、フェナントロリン誘導体（第43回高分子討論会予稿集、14J07などに記載のもの）などを挙げることができる。

本発明の有機ＥＬ素子に用いることのできる正孔注入材料、正孔輸送材料、発光材料および電子注入材料などには、好ましくはＴｇが８０℃以上のもの、より好ましくはＴｇが１００℃以上のものである。

本発明の有機ＥＬ素子の選択的構成層である界面層としては、陰極からの電子の注入を促進させられるものが好ましく、また陰極への正孔の流れ込みを阻止するものが好ましい。これらは、陰極に用いられる材料との相性によって選択され、その具体例としては、フッ化リチウム、フッ化マグネシウム、フッ化カルシウムなどが挙げられる。

本発明の有機ＥＬ素子を構成する各層は、各層を構成すべき材料を蒸着法、スピンコート法およびキャスト法などの公知の方法で薄膜とすることにより、形成することができる。

このようにして形成された各層の膜厚については特に制限はなく、素材の性質に応じて適宜選定することができるが、通常２ｎｍ～５０００ｎｍの範囲で選定される。

蒸着法を用いて薄膜化する場合、その蒸着条件は、ボラン誘導体の種類、分子累積膜の目的とする結晶構造及び会合構造などにより異なるが、一般に、ボート加熱温度５０～４００℃、真空度10^{-6}～10^{-3}Ｐａ、蒸着速度０．０１～５０ｎｍ／秒、基板温度－１５０～＋３００℃、膜厚５ｎｍ～５μｍの範囲で適宜選定することが望ましい。

次に、本発明の有機ＥＬ素子を作製する方法の一例として、前記構成（１）の陽極／ボラン誘導体層／陰極からなる有機ＥＬ素子の作製法について説明する。

適当な基板上に、陽極物質からなる薄膜を、１μｍ以下、好ましくは１０～２００ｎｍの範囲の膜厚になるように、蒸着法により形成させて陽極を作製した後、この陽極上にボラン誘導体の薄膜を形成させて発光層とし、この発光層の上に陰極物質からなる薄膜を蒸着法により、１μｍ以下の膜厚になるよう形成させて陰極とすることにより、目的の有機ＥＬ素子が得られる。

なお、上述の有機ＥＬ素子の作製においては、作製順序を逆にして、陰極、発光層、陽極の順に作製することも可能である。

この様にして得られた有機ＥＬ素子に直流電圧を印加する場合には、陽極を＋、陰極を－の極性として印加すれば良く、電圧２～４０Ｖ程度を印加すると、透明又は半透明の電極側（陽極又は陰極、及び両方）より発光が観測できる。

また、この有機ＥＬ素子は、交流電圧を印加した場合にも発光する。なお、印加する交流の波形は任意でよい。

発明を実施するための最良の形態

以下に実施例にて本発明を具体的に説明するが、本発明は下記の実施例に限定されるものではない。

＜ボラン誘導体の合成例＞

（実施例１）：前記の式（４）で表される化合物の合成

アルゴン気流下、９－ブロモアントラセンを５．１４ｇ含むエーテル溶液３０ｍｌに対し、ｎ－ブチルリチウム１．６mol/lのヘキサン溶液１３ｍｌを－７８℃設定下で加えた後、０℃まで昇温して３０分間攪拌し、続いて同温でボロントリフルオライド４．１ｍｌを含むエーテル溶液１０ｍｌに加え、１時間攪拌して黄色固体の析出物を得た。

その後、上澄みを除去し、乾燥エーテル３０ｍｌを添加して、１時間攪拌した後、再度上澄みを除去し、乾燥ＴＨＦ３０ｍｌを加えた。

更に、９，１０－ジリチオアントラセンのエーテル溶液を滴下し、室温で３時間攪拌して、析出物をろ過により除去し、ろ液を濃縮し、酢酸エチルを加え、析出物を酢酸エチルから再結晶し、目的の化合物を得た。その収率は４％であった。この化合物は、固体状態で赤色の蛍光を発した。

^{1}Ｈ－ＮＭＲ（C_6D_6）δ＝6.41(dd,4H)，6.77(t,8H)，7.06(t,8H)，7.77(d,8H)，8.35(s,4H)，8.59-8.63(m,12H).

（実施例２）：前記の式（６）で表される化合物の合成

実施例１で用いた９，１０－ジリチオアントラセンをメシチルリチウムに替えた以外は、実施例１に準ずる方法で合成した。

^{1}Ｈ－ＮＭＲ（C_6D_6）δ＝2.0(s,6H)，2.10(s,3H)，6.71(s,2H)，6.91(t,4H)，6.88-6.94(m,4H)，7.06-7.12(m,4H)，8.35(s,2H)，8.49(d,4H).

（実施例３）：前記の式（３）で表される化合物の合成

アルゴン気流下、９－ブロモアントラセンを５．１４ｇ含むエーテル溶液３０ｍｌに対し、ｎ－ブチルリチウム１．６mol/lのヘキサン溶液１３ｍｌを－７８℃設定下で加えた後、０℃まで昇温して３０分間攪拌し、続いて同温でボロントリフルオライド０．８ｍｌを含むエーテル溶液１０ｍｌに加え、１２時間攪拌して、橙色固体の析出物を得た。

析出物をベンゼンから再結晶し、目的の化合物を得た。その収率は３３％であ

った。

^{1}H－NMR（C_6D_6） δ＝6.83-6.89(m,6H)，7.21(t,4H)，7.95(d,6H)，8.12(d,6H)，8.58(s,4H).

＜有機ＥＬ素子の製造例およびその特性＞

（実施例４）

２５ｍｍ×７５ｍｍ×１．１ｍｍのガラス基板上にＩＴＯを蒸着法にて１００ｎｍの厚さに蒸着したもの（東京三容真空（株）製）を透明支持基板とした。この透明支持基板を市販の蒸着装置（真空機工（株）製）の基板ホルダーに固定しＮ，Ｎ’－ジナフチル－Ｎ，Ｎ’－ジフェニルベンジジン（以下ＮＰＤと略記する）をいれた石英るつぼ、前記の式（１０）で表される化合物を入れた石英るつぼ、１，１－ジメチル－２，５－ビス｛２－（２－ピリジル）ピリジル｝－３，４－ジフェニルシラシクロペンタジエン（以下、ＰＹＰＹという）を入れた石英るつぼ、マグネシウムを入れたグラファイト製のるつぼ、および銀を入れたグラファイト製のるつぼを装着した。

真空槽を１×１０$^{-3}$Ｐａまで減圧し、ＮＰＤ入りのるつぼを加熱して、膜厚５０ｎｍになるようにＮＰＤを蒸着して正孔輸送層を形成し、次いで、前記の式（１０）で表される化合物入りのるつぼを加熱して、膜厚１５ｎｍになるように蒸着して発光層を形成し、次いで、ＰＹＰＹ入りのるつぼを加熱して、膜厚３５ｎｍになるようにＰＹＰＹを蒸着して電子輸送層を形成した。蒸着速度は０．１～０．２ｎｍ／秒であった。

その後真空槽を２×１０$^{-4}$Ｐａまで減圧し、グラファイト製のるつぼを加熱して、マグネシウムを１．２～２．４ｎｍ／秒の蒸着速度で、同時に銀を０．１～０．２ｎｍ／秒の蒸着速度で蒸着し、有機層の上に１５０ｎｍのマグネシウムと銀の合金電極を形成することにより、有機ＥＬ素子を得た。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約１ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１００ｃｄ／ｍ^2、波長５１５ｎｍの緑色の発光を得た。

（比較例１）

前記の式（１０）で表される化合物をトリス（８－ヒドロキシキノリン）アルミニウムに替えた以外は、実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約１ｍＡ／ｃｍ^{2}の電流が流れ、輝度約２０ｃｄ／ｍ^2、波長５２２ｎｍの緑色の発光を得たが、実施例４に比べて、発光輝度が約１／５に低下した。

（比較例２）

前記の式（１０）で表される化合物をトリメシチルボランに替えた以外は、実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約５０ｍＡ／ｃｍ^{2}の電流が流れ、輝度約５ｃｄ／ｍ^{2}の紫色の発光を得たが、実施例４に比べて、発光輝度及び発光効率が大幅に低下した。

（実施例５）

実施例４で用いたＰＹＰＹを使用せずに、式（１０）で表される化合物からなる層の膜厚を５０ｎｍに替えた以外は、実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約１ｍＡ／ｃｍ^{2}の電流が流れ、輝度約６ｃｄ／ｍ^2、波長５１５ｎｍの緑色の発光を得た。

（実施例６）

実施例４で用いた式（１０）で表される化合物を、前記の式（４）で表される化合物に替えた以外は、実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約１ｍＡ／ｃｍ^{2}の電流が流れ、輝度約６ｃｄ／ｍ^2、波長６１６ｎｍの赤色の発光を得た。

（実施例７）

実施例４で用いた式（１０）で表される化合物を、前記の式（１１）で表される化合物に替えた以外は、実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約１ｍＡ／ｃｍ^{2}の電流が流れ、輝度約３０ｃｄ／ｍ^2、波長４６４ｎｍの青色の発光を得た。

（実施例８）

実施例４で用いた透明支持基板を蒸着装置の基板ホルダーに固定しＮＰＤをいれた石英るつぼ、式（１０）で表される化合物を入れた石英るつぼ、アルミニウムを入れたタングステン製のるつぼ、およびフッ化リチウムを入れたタングステン製のるつぼを装着した。

真空槽を１×１０$^{-3}$Ｐａまで減圧し、ＮＰＤ入りのるつぼを加熱して、膜厚５０ｎｍになるようにＮＰＤを蒸着して正孔輸送層を形成し、次いで、式（１０）で表される化合物入りのるつぼを加熱して、膜厚５０ｎｍになるように蒸着して電子輸送性発光層を形成した。蒸着速度は０．１～０．２ｎｍ／秒であった。

その後真空槽を２×１０$^{-4}$Ｐａまで減圧し、タングステン製のるつぼを加熱して、フッ化リチウムを２ｎｍ有機層の上に蒸着し、最後にアルミニウムを１００ｎｍ蒸着し、有機ＥＬ素子を得た。

ＩＴＯ電極を陽極、アルミニウム電極を陰極として、直流電圧を印加すると、約２ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１００ｃｄ／ｍ^2、波長５１５ｎｍの緑色の発光を得た。

（実施例９）

実施例８で用いた式（１０）で表される化合物を、式（４）で表される化合物に替えた以外は、実施例８に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約２ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１５ｃｄ／ｍ^2、波長６１６

ｎｍの赤色の発光を得た。

（実施例１０）

実施例４で用いた式（１０）で表される化合物を、前記の式（９）で表される化合物に替えた以外は、実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約２ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１００ｃｄ／ｍ^2、波長４７７ｎｍの青色の発光を得た。

（実施例１１）

実施例４で用いた式（１０）で表される化合物を、前記の式（１２）で表される化合物に替えた以外は実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約０．７ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１００ｃｄ／ｍ^2、波長５１１ｎｍの緑色の発光を得た。

（実施例１２）

実施例４で用いた式（１０）で表される化合物を、前記の式（１３）で表される化合物に替えた以外は実施例４に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約３０ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１００ｃｄ／ｍ^2、波長６２２ｎｍの赤色の発光を得た。

（実施例１３）

実施例４で用いた透明支持基板を蒸着装置の基板ホルダーに固定しＮＰＤをいれた石英るつぼ、式（１０）で表される化合物を入れた石英るつぼ、式（１１）で表される化合物を入れた石英るつぼ、ＰＹＰＹを入れた石英るつぼ、アルミニウムを入れたタングステン製のるつぼ、およびフッ化リチウムを入れたタングステン製のるつぼを装着した。

真空槽を1×10^{-3}Paまで減圧し、ＮＰＤ入りのるつぼを加熱して、膜厚５０ｎｍになるようにＮＰＤを蒸着して正孔輸送層を形成し、次いで、式（１０）および（１１）で表される化合物入りのるつぼを加熱して、膜厚１５ｎｍになるように蒸着して発光層を形成し、次いで、ＰＹＰＹ入りのるつぼを加熱して、膜厚３５ｎｍになるようにＰＹＰＹを蒸着して電子輸送層を形成した。この際、発光層のそれぞれの化合物の組成比は、式（１０）で表わされる化合物が２％、式（１１）で表わされる化合物が９８％になるようにした。

その後真空槽を2×10^{-4}Paまで減圧し、タングステン製のるつぼを加熱して、フッ化リチウムを０．５ｎｍ有機層の上に蒸着し、最後にアルミニウムを１００ｎｍ蒸着し、有機ＥＬ素子を得た。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約１ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１００ｃｄ／ｍ^2、波長４９５ｎｍの青緑色の発光を得た。

（実施例１４）

実施例１３で用いた式（１０）で表される化合物を式（１４）で表される化合物に、式（１１）で表される化合物をトリス８－ヒドロキシキノリンアルミニウムに替えた以外は、実施例１３に準ずる方法で素子を作成した。

ＩＴＯ電極を陽極、マグネシウムと銀の合金電極を陰極として、直流電圧を印加すると、約２０ｍＡ／ｃｍ^{2}の電流が流れ、輝度約１００ｃｄ／ｍ^2、波長約６００ｎｍの赤色の発光を得た。

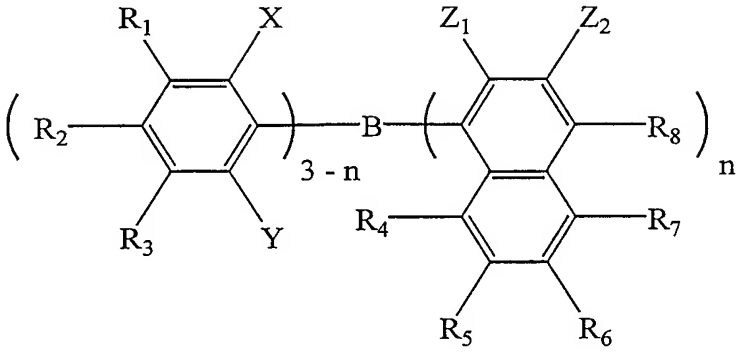
産業上の利用可能性

本発明の新規な化合物であるボラン誘導体は、固体状態での発光効率が高いので、発光材料として好適である。また、電子写真、非線形光学材料および導電性材料などの光電子機能材料としても有用である。

また、本発明の有機ＥＬ素子は、発光効率の高い発光材料を使用しているために、これを用いた場合、低消費電力で長寿命なディスプレイが作成できる。

請求の範囲

1．式（1）で表されるボラン誘導体。

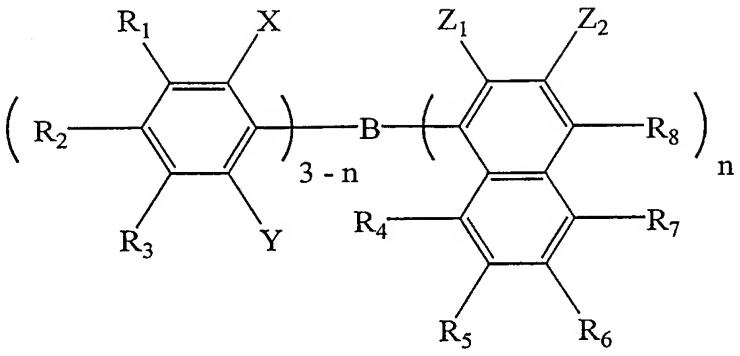


(1)

（式中、R_1～R_8およびZ_2は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、X、YおよびZ_1は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、Z_1とZ_2の置換基は相互に結合して縮合環を形成してもよく、nは1～3の整数を示し、nが2以上の場合、Z_1は異なってもよい。但し、nが1、X、YおよびR_2がメチル基であって、R_8が水素原子または置換ボリル基の場合、およびnが3でZ_1がメチル基の場合を含まない。）

2．ボロン原子に対して少なくとも1個の置換もしくは無置換の9－アンスリル基が結合している、請求項1に記載のボラン誘導体。

3．式（2）で表されるボラン誘導体を用いた発光材料。



(2)

（式中、R_1～R_8およびZ_2は、それぞれ独立に、水素原子、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、置換ボリル基、アルコキシ基またはアリールオキシ基を示し、X、YおよびZ_1は、それぞれ独立に、飽和もしくは不飽和の炭化水素基、芳香族基、ヘテロ環基、置換アミノ基、アルコキシ基またはアリールオキシ基を示し、Z_1とZ_2の置換基は相互に結合して縮合環を形成してもよく、nは1～3の整数を示し、nが2以上の場合、Z_1は異なってもよい。）

4．ボラン誘導体が、ボロン原子に対して少なくとも1個の置換もしくは無置換の9－アンスリル基が結合している化合物である、請求項3に記載の発光材料。

5．請求項3に記載の式（2）で表されるボラン誘導体を用いた電荷輸送材料。

6．ボラン誘導体が、ボロン原子に対して少なくとも1個の置換もしくは無置換の9－アンスリル基が結合している化合物である、請求項5に記載の電荷輸送材料。

7．請求項3に記載の式（2）で表されるボラン誘導体を用いた有機電界発光素子。

8．式（2）で表されるボラン誘導体の1種もしくは2種以上の混合物、または式（2）で表されるボラン誘導体の1種以上と式（2）で表されるボラン誘導体以外の発光材料の1種以上との混合物を発光層に用いた、請求項7に記載の有機電界発光素子。

9．式（2）で表されるボラン誘導体を電荷輸送層に用いた、請求項7に記載の

有機電界発光素子。

１０．ボラン誘導体が、ボロン原子に対して少なくとも１個の置換もしくは無置換の９－アンスリル基が結合している化合物である、請求項７乃至９のいずれか１項に記載の有機電界発光素子。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/07219

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07F5/02, C09K11/06, H05B33/14, H05B33/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07F5/02, C09K11/06, H05B33/14, H05B33/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	EP, 775706, A2 (Ciba Specialty Chemicals Holding Inc.), 28 May, 1997 (28.05.97) & JP, 9-188684, A & US, 5807905, A	1~2 3~10
X A	BLOUNT, John F. et al., "Conformational analysis of triarylboranes", J. Amer. Chem. Soc., 1973, Vol.95 No.21, p.7019-7029	1~2 3~10
A	WO, 98/36035, A1 (QUEEN'S UNIVERSITY AT KINGSTON), 20 August, 1998 (20.08.98) & AU, 9859780, B	1~10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 April, 2000 (03.04.00)	11 April, 2000 (11.04.00)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０７２１９

A.　発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int.Cl.[7]　C07F5/02, C09K11/06, H05B33/14, H05B33/22

B.　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int.Cl.[7]　C07F5/02, C09K11/06, H05B33/14, H05B33/22

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAPLUS(STN), REGISTRY(STN)

C.　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X A	EP,775706,A2(Ciba Specialty Chemicals Holding Inc.) 28.5月.1997(28.05.97) &JP,9-188684,A &US,5807905,A	1～2 3～10
X A	BLOUNT, John F. et al., "Conformational analysis of triarylboranes", J. Amer. Chem. Soc., 1973, Vol.95 No.21, p.7019-7029	1～2 3～10
A	WO,98/36035,A1(QUEEN'S UNIVERSITY AT KINGSTON) 20.8月.1998(20.08.98) &AU,9859780,B	1～10

☐ Ｃ欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
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「Y」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日 ０３．０４．００	国際調査報告の発送日 11.04.00
国際調査機関の名称及びあて先 日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	特許庁審査官（権限のある職員） 本堂　裕司　印　4H　9049 電話番号　０３－３５８１－１１０１　内線　３４４３

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(19) World Intellectual Property Organization
International Bureau

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(25) Filing Language: English

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60/151,875	31 August 1999 (31.08.1999)	US

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(74) Agent: **VIKSNINS, Ann, S.**; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).

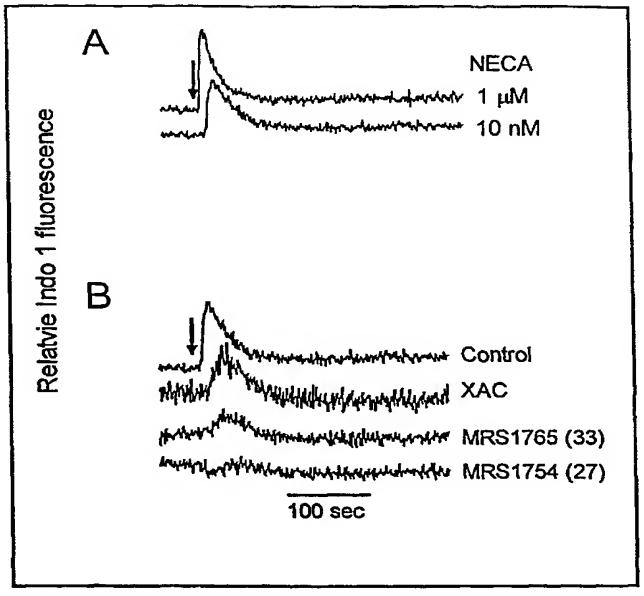
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

[Continued on next page]

(54) Title: SUBSTITUTED 8-PHENYLXANTHINES USEFUL AS ANTAGONISTS OF A_{2B} ADENOSINE RECEPTORS



(57) Abstract: The present invention provides compounds and pharmaceutical compositions that are selective antagonists of A_{2B} adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.

WO 00/73307 A2

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SUBSTITUTED 8-PHENYLXANTHINES USEFUL AS ANTAGONISTS OF A_{2B} ADENOSINE RECEPTORS

Cross-Reference to Related Applications

This application claims priority of U.S. provisional patent applications Serial Nos. 60/136,898 filed June 1, 1999, 60/136,900 filed June 1, 1999, 60/151,875 filed August 31, 1999, and 09/505,504 filed February 17, 2000.

Government Funding

The invention described herein was made with government support under Grant Numbers HL37942 and HL56111 awarded by the National Institute of Health. The United States Government has certain rights in the invention.

Field of the Invention

The present invention relates to compounds and pharmaceutical compositions that are selective antagonists of A_{2B} adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.

Background of the Invention

The alkylxanthine theophylline (compound **1**, Figure 1), a weak non-selective adenosine antagonist (See Linden, J., *et al.*,. in *Cardiovascular Biology of Purines*, eds. G. Burnstock, *et al.*, **1998**, pp 1-20.) is useful therapeutically for the treatment of asthma. However, its use is associated with unpleasant side effects, such as insomnia and diuresis. (See Vassallo, R. *et al.*, *Mayo. Clin. Proc.* **1998**, *73*, 346-354.) In recent years, the use of theophylline as a bronchodilator, for relief of asthma, has been supplanted by drugs of other classes, *i.e.*, selective β_2-adrenergic agonists, corticosteroids, and recently leukotriene antagonists. (See Drazen, J. M., *et al.*, *New Eng. J. Med.* **1999**, *340*, 197-206.) These compounds also have limitations, thus, the development of a theophylline-like drug with reduced side effects is still desirable.

It has been recognized that theophylline and its closely related analogue caffeine block endogenous adenosine acting as a local modulator of adenosine

receptors in the brain and other organs at therapeutically useful doses. Adenosine activates four subtypes of G protein-coupled adenosine receptors (ARs), $A_1/A_{2A}/A_{2B}/A_3$. (See Fredholm, B. B., *et al.*, *Pharmacol. Rev.* **1999**, *51*, 83-133.) In comparison to the other known actions of theophylline, *e.g.*, inhibition of phosphodiesterases, theophylline is more potent in antagonism of adenosine receptors. Enprofylline, (compound **3**, Figure 1) a compound that is used to treat asthma, is another example of a xanthine that has been reported to block A_{2B} adenosine receptors. However, this compound only weakly blocks A_1, A_{2A} and A_3 adenosine receptors.

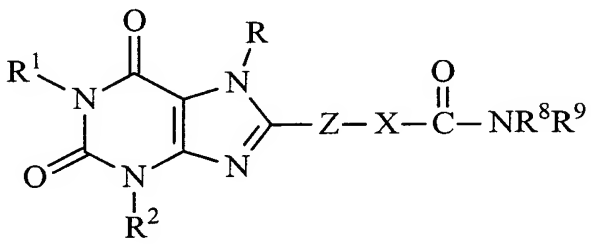
It has been reported that therapeutic concentrations of theophylline or enprofylline block human A_{2B} receptors, and it has been proposed that antagonists selective for this subtype may have potential use as antiasthmatic agents. (See Feoktistov, I., *et al.*, *Pharmacol. Rev.* **1997**, *49*, 381-402; and Robeva, A.S., *et al.*, *Drug Dev. Res* . **1996**, *39*, 243-252. Enprofylline has a reported K_i value of 7 μM and is somewhat selective in binding to human A_{2B} ARs. (See Robeva, A.S., *et al.*, *Drug Dev. Res* . **1996**, *39*, 243-252 and Linden, J., *et al.*,. *Mol. Pharmacol.* **1999**, *56*, 705-713.) A_{2B} ARs are expressed in some mast cells, such as the BR line of canine mastocytoma cells, which appear to be responsible for triggering acute Ca^{2+} mobilization and degranulation. (See Auchampach, J.A., *et al.*, *Mol. Pharmacol* . **1997**. *52*, 846-860 and Forsyth, P., *et al.*, *Inflamm. Res.* **1999**, *48*, 301-307.) A_{2B} ARs also trigger Ca^{2+} mobilization, and participate in a delayed IL8 release from human HMC-1 mast cells. Other functions associated with the A_{2B} AR are the control of cell growth and gene expression, (See Neary, J., *et al.*, *Trends Neurosci.* **1996**, *19*, 13-18.) endothelial-dependent vasodilation (See Martin, P.L., *et al.*, *J. Pharmacol. Exp. Ther.* **1993**, *265*, 248-253.), and fluid secretion from intestinal epithelia. (See Strohmeier, G.R., *et al.*, *J. Biol. Chem.* **1995**, *270*, 2387-2394.) Adenosine acting through A_{2B} ARs has also been reported to stimulate chloride permeability in cells expressing the cystic fibrosis transport regulator. (See Clancy, J.P., *et al.*, *Am. J. Physiol.* **1999**, *276*, C361-C369.)

Although adenosine receptor subtype-selective probes are available for the A_1, A_{2A}, and A_3 ARs, only few weakly selective antagonists and no selective

agonists are known for the A_{2B} receptor. Therefore, a continuing need exists for compounds that are selective A_{2B} receptor antagonists.

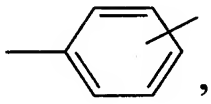
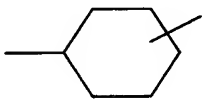
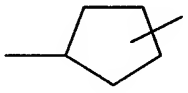
Summary of the Invention

The present invention provides compounds that act as antagonists of A_{2B} adenosine receptors. Accordingly, the present invention provides a compound of formula I:



I

wherein R, and R^1 are independently hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_4\text{-}C_{16})$cycloalkylalkyl, heterocycle, $(C_6\text{-}C_{10})$aryl, $(C_7\text{-}C_{18})$aralkyl or heteroaryl;

Z is  ,  , or  ;

X is $(C_1\text{-}C_8)$alkylene, $(C_2\text{-}C_8)$alkenylene, $(C_2\text{-}C_8)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups can be replaced with a group having the formula —O—, —$N(R^4)C(O)$—, —OC(O)—, —$N(R^5)(R^6)$—, —S—, —S(O)— or —SO_2—, wherein

R^2 is hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$heterocycle, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$heteroaryl, $(C_4\text{-}C_{16})$cycloalkylalkyl or $(C_7\text{-}C_{18})$aralkyl, optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —CO_2H, and —SO_3H, wherein

R^4, R^5, R^6 and R^7 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl,

wherein R^8 is hydrogen, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^9 is —$NR^{10}R^{11}$, or R^9 is $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2,

—CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H, and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, heteroaryl, —$C(O)(CH_2)_nCO_2R^{12}$, —$C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, —$C(O)R^{12}$, —$C(O)$($C_3$-$C_8$)cycloalkyl or —$C(O)$($C_3$-$C_8$)cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})-aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H.

The R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{23} and R^{24} groups are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl; and the R^{21} and R^{22} groups are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl.

The invention also provides pharmaceutically acceptable salts of a compound of formula I. The invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically

acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

Additionally, the invention provides a therapeutic method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity, *i.e.*, over-activity, of adenosine A_{2B} receptors is implicated in one or more symptoms of the pathology and antagonism (*i.e.*, blocking) of their activity is desired to ameliorate said symptoms. Such diseases or conditions include, but are not limited to, asthma, diarrheal diseases, insulin resistance, diabetes, prevention of mast cell degranulation associated with ischemia/reperfusion injuries, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy. The invention also includes a method for treating asthma, diarrheal diseases, insulin resistance, diabetes, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy in a mammal, (*e.g.*, a human) comprising administering to the mammal in need of such therapy, an effective amount of at least one compound of formula I or pharmaceutically acceptable salt(s) thereof.

The invention provides a compound of formula I for use in medical therapy preferably for use in treating diseases or conditions associated with deleterious A_{2B} receptor activation or activity, including asthma, diarrheal diseases, insulin resistance, diabetes, ischemic/reperfusion injury, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy, as well as the use of a compound of formula I for the manufacture of a medicament for the treatment of a pathological condition or symptom in a mammal, such as a human, which is associated with deleterious A_{2B} receptor activation or activity, including the above-referenced diseases or pathologies.

The invention also includes a method comprising contacting a compound of formula I, optionally having a radioactive isotope (radionuclide), such as, for example, tritium, radioactive iodine (for example, ^{125}I for binding assays or ^{123}I for Spect Imaging) and the like, with target A_{2B} adenosine receptor sites comprising said receptors, *in vivo* or *in vitro*, so as to bind said receptors. Cell membranes comprising bound A_{2B} adenosine receptor sites can be used to

measure the selectivity of test compounds for adenosine receptor subtypes or can be used as a tool to identify potential therapeutic agents for the treatment of diseases or conditions associated with A_{2B}-receptor mediation, by contacting said agents with said radioligands and receptors, and measuring the extent of displacement of the radioligand and/or binding of the agent.

Brief Description of the Figures

Figure 1 illustrates structures of various xanthines that act as antagonists at A_{2B} receptors.

Figure 2 is a graphic illustration of the inhibition by several selective A_{2B} AR antagonists of NECA-stimulated calcium mobilization in HEK-A_{2B} cells. Cells were loaded with Indo 1 for 1 hour. The A) curves indicate calcium mobilization in response to 10 nM and 1 μM NECA added at the arrow. The B) curves indicate calcium mobilization in response to 10 nM NECA added at the arrow in cells pretreated for two minutes with 1% DMSO (control) or with 100 nM of the indicated antagonists. The results are typical of replicate experiments.

Figure 3 illustrates the synthesis of amide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 4 illustrates the synthesis of hydrazide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 5 illustrates the synthesis of hydrazide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 6 illustrates the experimental protocol for the ninety minute cardiac left anterior descending (LAD) coronary artery occlusion/reperfusion test. Regional myocardial blood flow was measured at 30 second, 90 second, 3 minute, 5 minute, 8 minute, 13 minute, 23 minute, 38 minute, and 68 minute, intervals, using radioactive microspheres (mic), administered at the times indicated.

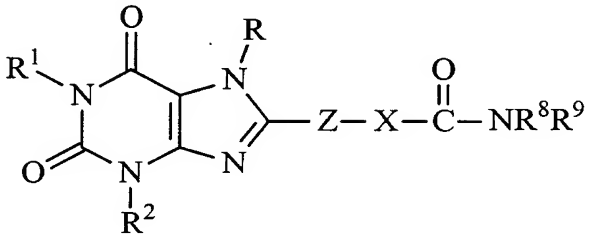
Figure 7 illustrates the regional myocardial transmural blood flow in the central infarct (solid bar), border (open bar), and normal (striped bar) zones at baseline, during the LAD occlusion, and 2 hrs after reperfusion. During the total LAD occlusion, mean flow of test solution was < 0.2 ml/min/g for 90 min.

Figure 8 illustrates the mean infarct size measured using triphenyl tetrazolium chloride (TTC) staining in vehicle-treated (control) dogs and in dogs treated with 8-[4-[((4-cyano)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (**27**). The *p*-cyanoanilide, **27**, (200 nM) was infused intracoronary at a rate of 1 ml/min during occlusion and reperfusion. The treatment prevented or markedly attenuate the extent of myocardial infarction and significantly reduced the infarct area (IA), measured as % left ventricle area (%LV) or % area at risk (%RA).

Figure 9 illustrates the results the specific and nonspecific binding of test compound 8-[4-[((4-cyano)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (**27**). The graph shows both specific and nonspecific binding.

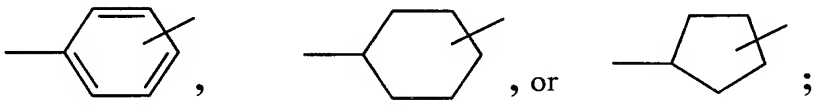
Detailed Description of the Invention

In one embodiment the present invention provides compounds of formula I:



I

wherein R, and R^1 are independently hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_4\text{-}C_{16})$cycloalkylalkyl, $(C_3\text{-}C_8)$heterocycle, $(C_6\text{-}C_{10})$aryl, $(C_7\text{-}C_{18})$aralkyl or $(C_6\text{-}C_{10})$heteroaryl,

Z is  ;

and X is $(C_1\text{-}C_8)$alkylene, $(C_2\text{-}C_8)$alkenylene, $(C_2\text{-}C_8)$alkynylene. In the X groups one of the carbon atoms in the alkylene, alkenylene or alkynylene groups can be

replaced with a group having the formula —O—, —N(R^4)C(O)—, —OC(O)—, —N(R^5)(R^6)—, —S—, —S(O)— or —SO_2—, wherein

R^2 is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_3-C_8)heterocycle, (C_6-C_{10})aryl, (C_6-C_{10})heteroaryl, (C_4-C_{16})cycloalkylalkyl or (C_7-C_{18})aralkyl; optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —CO_2H, and —SO_3H, wherein

R^4, R^5, R^6 and R^7 are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl.

R^8 is hydrogen, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} and —SO_3H; and

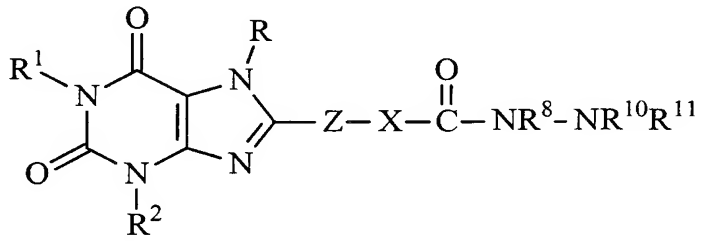
wherein R^9 is (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H.

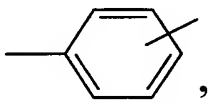
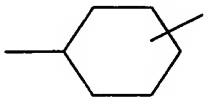
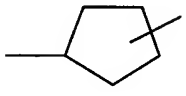
The R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{23} and R^{24} groups are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl.

In another embodiment the present invention provides compounds of formula II:



II

wherein R, and R^1 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_3$-$C_8)$heterocycle, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or $(C_6$-$C_{10})$heteroaryl,

Z is  ,  , or  ;

and X is $(C_1$-$C_8)$alkylene, $(C_2$-$C_8)$alkenylene, $(C_2$-$C_8)$alkynylene. In the X groups one of the carbon atoms in the alkylene, alkenylene or alkynylene groups can be

replaced with a group having the formula —O—, —N(R^4)C(O)—, —OC(O)—, —N(R^5)(R^6)—, —S—, —S(O)— or —SO_2—, wherein

R^2 group is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_3-C_8)heterocycle, (C_6-C_{10})aryl, (C_6-C_{10})heteroaryl, (C_4-C_{16})cycloalkylalkyl or (C_7-C_{18})aralkyl; optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —CO_2H, and —SO_3H, wherein R^4, R^5 R^6 and R^7 are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl.

R^8 is hydrogen, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —C(O)(CH_2)$_n$$CO_2$R^{12}, —C(O)CR^{21}=CR^{22}(CH_2)$_m$$CO_2$R^{12}, —C(O)R^{12}, —C(O)(C_3-C_8)cycloalkyl or —C(O)(C_3-C_8)cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} or

—SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H.

The R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18},R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl; and the R^{21} and R^{22} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl.

Preferred compounds of the invention exclude compounds of formula I wherein —NR^8R^9 is aminoalkyl, aminodialkyl or hydrazino. Preferred compounds of the invention also exclude and compounds of formula I wherein R and R^8 are both H, and R^1 and R^2 are both alkyl, and R^9 is 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such

as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing 5-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, $(C_1$-$C_4)$alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene or tetramethylene diradical thereto.

The term heterocycle encompasses a cyclic radical attached via a ring carbon or nitrogen of a monocyclic or bicyclic ring containing 3-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, $(C_1$-$C_4)$alkyl, phenyl or benzyl, and optionally containing 1-3 double bonds (*e.g.*, —CH=CH— or —CH=N—). Heterocycle includes, for example, tetrahydrofuryl, dihydrofuryl, tetrahydro-imidazolyl, azanorbornyl, pyrrolidinyl, piperidinyl, piperizinyl, and the like.

Specifically, $(C_1$-$C_8)$alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, isopentyl, 3-pentyl, hexyl, heptyl or octyl; $(C_3$-$C_8)$cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; $(C_4$-$C_{12})$cycloalkylalkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl or 2-cyclohexylethyl; $(C_1$-$C_8)$alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy, heptyloxy or octyloxy; $(C_2$-$C_8)$alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1- heptenyl, 2-heptenyl, 3-heptenyl, 1- octenyl, 2-octenyl, 3-octenyl or 4-octenyl; $(C_2$-$C_8)$alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1- heptynyl, 2-heptynyl, 3-heptynyl, 1- octynyl, 2-octynyl or 3-octynyl; halo$(C_1$-$C_6)$alkyl can be

iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl or pentafluoroethyl; (C_6-C_{10})aryl can be phenyl, indenyl or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

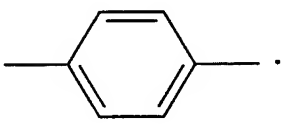
The term "amino acid," comprises the residues of the natural amino acids (*e.g.*, Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well as unnatural amino acids (*e.g.*, phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline, α-methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term also comprises natural and unnatural amino acids bearing a conventional amino protecting group (*e.g.*, acetyl, benzyl, $COCF_3$ or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus (*e.g.*, as a (C_1-C_6)alkyl, phenyl or benzyl ester or amide; or as an α-methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, Greene, T.W.; Wutz, P.G.M. *Protecting Groups In Organic Synthesis,* Second Edition, 1991, New York, John Wiley & sons, Inc, and references cited therein). An amino acid can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine.

The term "peptide" comprises the residues two or more of the natural amino acids, as well as unnatural amino acids or a mixture thereof, that are linked through an amide bond. The term also comprises peptides that are protected at the carboxy terminus (*e.g.*, as a (C_1-C_6)alkyl, phenyl or benzyl ester or amide; or as an α-methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, Greene, T.W.; Wutz, P.G.M. *Protecting Groups In Organic Synthesis,* Second Edition, 1991, New York, John Wiley & sons, Inc, and references cited therein). A

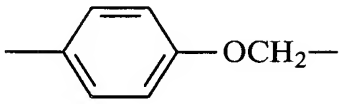
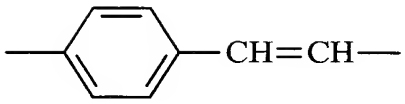
peptide can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine. Preferably, the peptide has less than 30 amino acid residues, more preferably less than 20 residues, and most preferably from about 2 to about 5 residues.

The preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, iso-butyl, and sec-butyl, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, and 3-hexyl. The preferred alkylene groups are methylene, ethylene, propylene, butylene, pentylene, and hexylene. The preferred alkenyl groups are vinyl, 1-propenyl, 2-propenyl (allyl), 1-butenyl, 2-butenyl, 3-butenyl, 1,-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1- hexenyl, 2-hexenyl, and 3-hexenyl. The preferred alkenylene groups are ethenylene, propenylene, butenylene, pentenylene, and hexenylene. The preferred alkynyl groups are ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl. The preferred alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, and sec-butoxy. The preferred cycloalkyl groups are cyclopentyl, and cyclohexyl. The preferred cycloalkylalkyl groups are, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentylethyl, and 2-cyclohexylethyl. The preferred aryl groups are phenyl, indenyl or naphthyl. The preferred aralkyl groups are benzyl and 2-phenylethyl. The preferred haloalkyl groups are iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl or pentafluoroethyl. The preferred heteroaryl groups are furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, thiodiazolyl, thiophenyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridinyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

A specific Z substituent is :



A specific Z—X moiety is:

 or  .

Specific R^1 and R^2 groups are each $—CH_2CH_3$, $—CH_2CH=CH_2$, $—CH_2CH_2CH_3$ or cyclohexylmethyl.

Specific R^8 and R^9 groups are each hydrogen, substituted phenyl or benzyl.

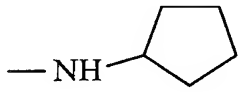
Specific R^4, R^5, R^6, and R^7 groups are each hydrogen, methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl and benzyl.

In a preferred embodiment, when the R^9 groups are phenyl substituted with one two or three substituents that are independently cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl, benzyl, —OH, F, Cl, Br, I, —CN, $—NO_2$, $—C(O)OR^{15}$, $—C(O)R^{16}$, $—NR^{13}R^{14}$ or $—C(O)NR^{17}R^{18}$ or benzyl they can optionally be methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl, benzyl, —OH, F, Cl, Br, I, —CN, $—NO_2$, $—C(O)OR^{15}$, $—C(O)R^{16}$ or $—C(O)NR^{17}R^{18}$, wherein R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} are as defined above.

The preferred R^{10}, and R^{11} groups are hydrogen, methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl and benzyl, $—CO(CH_2)_nCO_2R^{12}$, $—COCR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, $—C(O)R^{12}$, $—C(O)(C_3\text{-}C_8)$cycloalkyl, $—C(O)(C_3\text{-}C_8)$cycloalkenyl, and compounds wherein the R^{10} and R^{11} groups and the nitrogen atom taken together form a ring. More preferred R^{10}, and R^{11} groups are independently hydrogen, $—CO(CH_2)_nCO_2R^{12}$, $—COCR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, $—C(O)R^{12}$, $—C(O)(C_3\text{-}C_6)$cycloalkyl and $—C(O)(C_3\text{-}C_6)$cycloalkenyl, each wherein the R^{10} and R^{11} groups and the nitrogen atom taken together form $(C_6\text{-}C_{10})$heterocycle or $(C_6\text{-}C_{10})$heteroaryl, n is 1 to 4 and m is 0 to 2. The most preferred R^{10}, and R^{11} groups are independently hydrogen, $—CO(CH_2)_nCO_2R^{12}$, $—COCH=CHCO_2R^{12}$, $—C(O)R^{12}$, or wherein the R^{10} and R^{11} groups and the nitrogen atom taken

together form a ring or wherein n is 1 to 4 and R^{12}, R^{13}, R^{14}, R^{21} and R^{22} are defined above.

Specific values for —NR^8R^9 are: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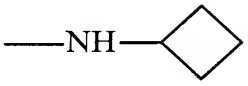
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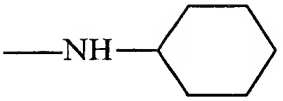
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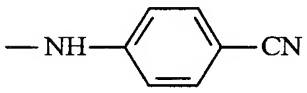
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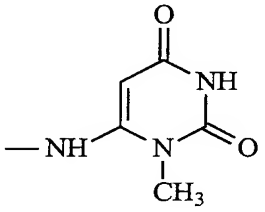
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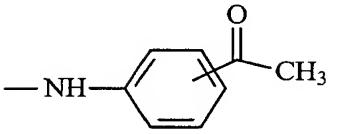
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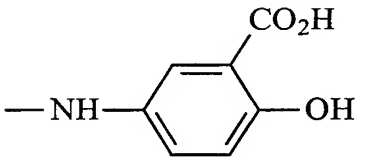
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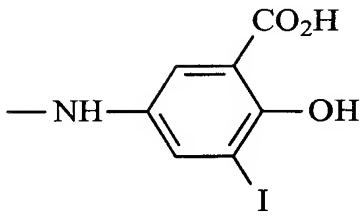
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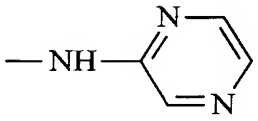
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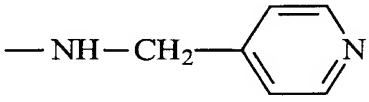
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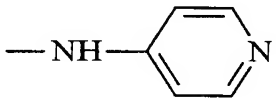
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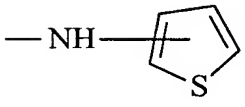
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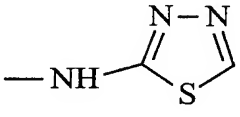
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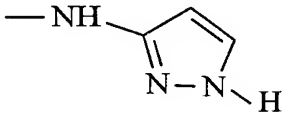
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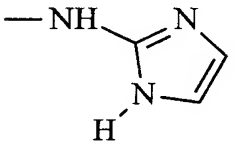
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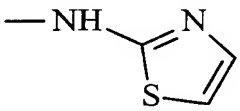
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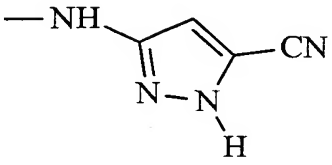
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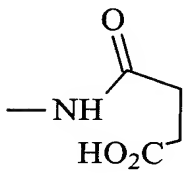
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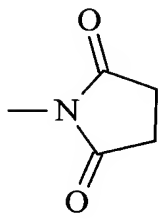
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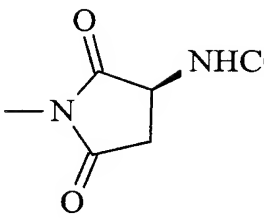
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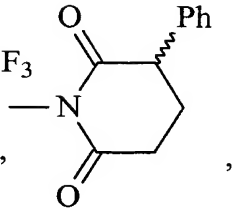
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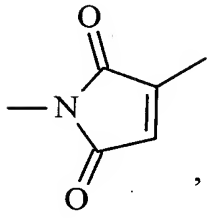
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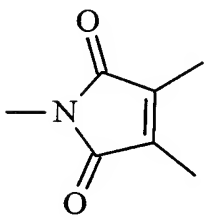
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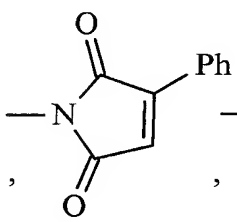
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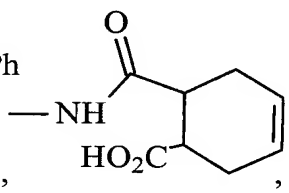
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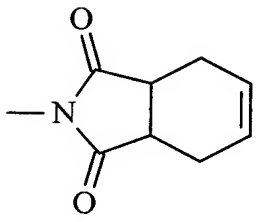
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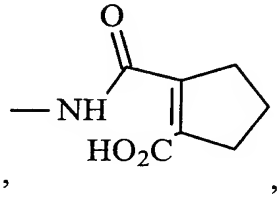
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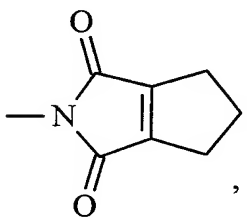
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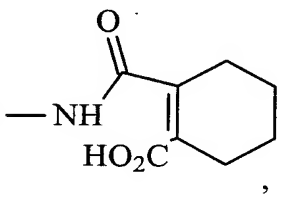
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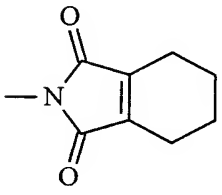
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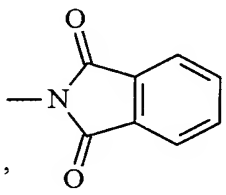
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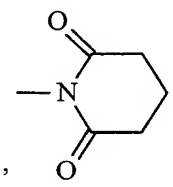
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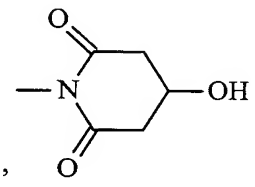
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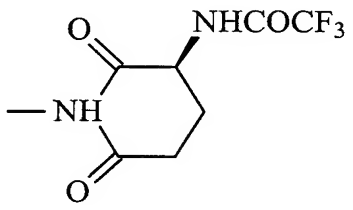
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The following abbreviations have been used herein:

[^{125}I]ABA	[^{125}I]N^6-(4-aminobenzyl)-adenosine
[^{125}I]AB-MECA	[^{125}I]N^6-(4-amino-3-iodobenzyl)-adenosine-5′-*N*-methyluronamide
^{125}I-ABOPX	^{125}I-3-(4-amino-3-iodobenzyl)-8-oxyacetate-1-propyl-xanthine
8-SPT	8-sulfophenyltheophylline
AR	adenosine receptor
Bn	benzyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
CGS 21680	2-[4-[(2-carboxyethyl)phenyl]ethyl-amino]-5′-*N*-ethylcarbamoyl adenosine
CHA	N^6-cyclohexyladenosine
CHO cells	Chinese hamster ovary cells
CPX	8-cyclopentyl-1,3-dipropylxanthine
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMEM	Dulbecco modified eagle medium
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EDAC	1-ethyl-3-(3-dimethlyaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetate
HEK cells	human embryonic kidney cells
HOBt	1-hydroxybenzotriazole
K_i	equilibrium inhibition constant
NECA	5Ì-(*N*-ethylcarbamoyl)adenosine
NHS	N-hydroxysuccinimide ester
R-PIA	*R*-N^6-phenylisopropyladenosine
SAR	structure-activity relationship
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Tris	tris(hydroxymethyl)aminomethane

XAC	8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine
XCC	8-[4-[[[carboxy]methyl]oxy]phenyl]-1,3-dipropylxanthine
ZM 241385	4-(2-[7-amino-2-{furyl}{1,2,4}triazolo{2,3-a}{1,3,5}triazin-5-ylaminoethyl)phenol

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis or by chromatographic separation using a chiral stationary phase). It is also conventional to determine A_{2B} adenosine antagonist activity using the standard tests described herein or using other similar tests which are well known in the art.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *i.e.*, orally or parenterally, by intravenous, intramuscular, topical, inhalation or subcutaneous routes.

Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and

substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying

techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, *i.e.*, when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet *et al.* (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith *et al.* (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the compound or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected

but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 μg/kg, *e.g.*, from about 10 to about 75 μg/kg of body weight per day, such as 3 to about 50 μg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 μg/kg/day, most preferably in the range of 15 to 60 μg/kg/day.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 μg, conveniently 10 to 750 μg, most conveniently, 50 to 500 μg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.02, to about 5 μM, preferably, about 0.05 to 2 μM, most preferably, about 0.1 to about 1 μM. This may be achieved, for example, by the intravenous injection of a 0.005 to 0.5% solution of the active ingredient, optionally in saline or orally administered as a bolus containing about 1-100 μg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-0.1 μg/kg/hr or by intermittent infusions containing about 1-10 μg/kg of the active ingredient(s).

The compounds of the invention can be administered by inhalation from an inhaler, insufflator, atomizer or pressurized pack or other means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as carbon dioxide or other suitable gas. In case of a pressurized aerosol, the dosage unit may be determined by providing a value to deliver a metered amount. The inhalers, insufflators, atomizers are fully described in pharmaceutical reference books such as Remington's Pharmaceutical Sciences Volumes 16 (1980) or 18 (1990) Mack Publishing Co.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple

inhalations from an insufflator or by application of a plurality of drops into the eye.

The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

Pharmacology.

The ability of a compounds of the invention to act as an A_{2B} adenosine receptor antagonists may be determined using pharmacological models which are well known to the art or using test procedures described below.

The human A_{2B} receptor cDNA was subcloned into the expression plasmid pDoubleTrouble as described in Robeva, A. *et al.*, Biochem. Pharmacol., 51, 545-555 (1996). The plasmid was amplified in competent JM109 cells and plasmid DNA isolated using Wizard Megaprep columns (Promega Corporation, Madison, WI). A_{2B} adenosine receptors were introduced into HEK-293 cells by means of Lipofectin as described in Felgner, P. L. *et al.*, Proc. Natl. Acad. Sci. USA, 84, 7413-7417 (1987).

Cell culture

Transfected HEK cells were grown under 5% CO_2/95% O_2 humidified atmosphere at a temperature of 37°C. Colonies were selected by growth of cells in 0.6 mg/mL G418. Transfected cells were maintained in DMEM supplemented with Hams F12 nutrient mixture (1/1), 10% newborn calf serum, 2 mM glutamine and containing 50 IU/mL penicillin, 50 mg/mL streptomycin, and 0.2 mg/mL Geneticin (G418, Boehringer Mannheim). Cells were cultured in 10 cm diameter round plates and subcultured when grown confluent (approximately after 72 hours).

Radioligand binding studies.

At A_{2B} receptors: Confluent monolayers of HEK-A_{2B} cells were washed with PBS followed by ice cold Buffer A (10 mM HEPES, 10 mM EDTA, pH 7.4) with protease inhibitors (10 μg/mL benzamidine, 100 μM phenylmethanesulfonyl fluoride, and 2 μg/mL of each aprotinin, pepstatin and

leupeptin). The cells were homogenized in a Polytron (Brinkmann) for 20 s, centrifuged at 30,000 x g, and the pellets washed twice with buffer HE (10 mM HEPES, 1 mM EDTA, pH 7.4 with protease inhibitors). The final pellet was resuspended in buffer HE, supplemented with 10% sucrose and frozen in aliquots at -80°C. For binding assays membranes were thawed and diluted 5-10 fold with HE to a final protein concentration of approximately 1 mg/mL. To determine protein concentrations, membranes, and bovine serum albumin standards were dissolved in 0.2% NaOH/0.01% SDS and protein determined using fluorescamine fluorescence. Stowell, C. P. *et al.*, Anal. Biochem., 85, 572-580 (1978).

Saturation binding assays for human A_{2B} adenosine receptors were performed with [^{3}H]ZM214,385 (17 Ci/mmol, Tocris Cookson, Bristol UK) (Ji, X. *et al.*, Drug Design Discov., 16, 216-226 (1999)) or ^{125}I-ABOPX (2200 Ci/mmol). To prepare ^{125}I-ABOPX, 10 µL of 1 mM ABOPX in methanol/1 M NaOH (20:1) was added to 50 µL of 100 mM phosphate buffer, pH 7.3. One or 2 mCi of Na^{125}I was added, followed by 10 µL of 1 mg/mL chloramine-T in water. After incubation, 20 minutes at room temperature, 50 µL of 10 mg/mL Na-metabisulfite in water was added to quench the reaction. The reaction mixture was applied to a C18 HPLC column, eluting with a mixture of methanol and 5 mM phosphate, pH 6.0. After 5 min at 35% methanol, the methanol concentration was ramped to 100% over 15 min. Unreacted ABOPX eluted in 11-12 minutes; ^{125}I-ABOPX eluted at 18-19 min in a yield of 50-60% with respect to the initial ^{125}I.

In equilibrium binding assays the ratio of ^{127}I/^{125}I-ABOPX was 10-20/1. Radioligand binding experiments were performed in triplicate with 20-25 µg membrane protein in a total volume of 0.1 mL HE buffer supplemented with 1 U/mL adenosine deaminase and 5 mM $MgCl_2$. The incubation time was 3 h at 21°C. Nonspecific binding was measured in the presence of 100 µM NECA. Competition experiments were carried out using 0.6 nM ^{125}I-ABOPX. Membranes were filtered on Whatman GF/C filters using a Brandel cell harvester (Gaithersburg, MD) and washed 3 times over 15-20 seconds with ice cold buffer (10 mM Tris, 1 mM $MgCl_2$, pH 7.4). B_{max} and K_D values were calculated by Marquardt's nonlinear least squares interpolation for single a site

binding models. Marquardt, D. M., J. Soc. Indust. Appl. Math., 11, 431-441.21 (1963). K_i values for different compounds were derived from IC_{50} values as described. Linden, J., J. Cycl. Nucl. Res., 8, 163-172 (1982).

Data from replicate experiments are tabulated as means ± SEM.

At other Adenosine Receptors:

[^{3}H]CPX. Bruns, R. F. *et al.*, Naunyn-Schmiedeberg's Arch. Pharmacol., 335, 59-63 (1987). ^{125}I-ZM241385 and ^{125}I-ABA were utilized in radioligand binding assays to membranes derived from HEK-293 cells expressing recombinant human A_1, A_{2A} and A_3 ARs, respectively. Binding of [^{3}H]*R*-N^6-phenylisopropyladenosine. Schwabe, U. *et al.*, Naunyn-Schmiedeberg's Arch. Pharmacol., 313, 179-187 (1980). ([^{3}H]*R*-PIA, Amersham, Chicago, IL) to A_1 receptors from rat cerebral cortical membranes and of [^{3}H]CGS 21680. Jarvis, M.F. *et al.*, J. Pharmacol. Exp. Therap., 251, 888-893 (1989). (Dupont NEN, Boston, MA) to A_{2A} receptors from rat striatal membranes was performed as described. Adenosine deaminase (3 units/mL) was present during the preparation of the brain membranes, in a pre-incubation of 30 min at 30°C, and during the incubation with the radioligands. All non-radioactive compounds were initially dissolved in DMSO, and diluted with buffer to the final concentration, where the amount of DMSO never exceeded 2%. Incubations were terminated by rapid filtration over Whatman GF/B filters, using a Brandell cell harvester (Brandell, Gaithersburg, MD). The tubes were rinsed three times with 3 mL buffer each.

At least six different concentrations of competitor, spanning 3 orders of magnitude adjusted appropriately for the IC_{50} of each compound, were used. IC_{50} values, calculated with the nonlinear regression method implemented in (Graph-Pad Prism, San Diego, CA), were converted to apparent K_i values as described. Linden, J., J. Cycl. Nucl. Res., 8:163-172 (1982). Hill coefficients of the tested compounds were in the range of 0.8 to 1.1.

Functional assay:

HEK-A_{2B} cells from one confluent T75 flask were rinsed with Ca^{2+} and Mg^{2+} -free Dulbecco's phosphate buffered saline (PBS) and then incubated in Ca^{2+} and Mg^{2+} - free HBSS with 0.05% trypsin and 0.53 mM EDTA until the cells detached. The cells were rinsed twice by centrifugation at 250 x g in PBS and resuspended in 10 mL of HBSS composed of 137 mM NaCl, 5 mM KCl, 0.9 mM $MgSO_4$, 1.4 mM $CaCl_2$, 3 mM $NaHCO_3$, 0.6 mM Na_2HPO_4, 0.4 mM KH_3PO_4, 5.6 mM glucose, and 10 mM HEPES, pH 7.4 and the Ca^{2+}-sensitive fluorescent dye indo-1-AM (5 μM) 37° for 60 min. The cells were rinsed once and resuspended in 25 mL dye-free HBSS supplemented with 1 U/ml adenosine deaminase and held at room temperature. Adenosine receptor antagonists prepared as 100X stocks in DMSO or vehicle was added and the cells and transferred to a 37° bath for 2 minutes. Then the cells (1 million in 2 ml) were transferred to a stirred cuvette maintained at 37° within an Aminco SLM 8000 spectrofluorometer (SML instruments, Urbana IL). The ratios of indo-1 fluorescence obtained at 400 and 485 nm (excitation, 332 nm) was recorded using a slit width of 4 nm. NECA was added after a 100 s equilibration period.

Cyclic AMP accumulation

Cyclic AMP generation was performed in DMEM/HEPES buffer (DMEM containing 50 mM HEPES, pH 7.4, 37°C). Each well of cells was washed twice with DMEM/HEPES buffer, and then 100 μL adenosine deaminase (final concentration 10 IU/mL) and 100 μL of solutions of rolipram and cilostamide (each at a final concentration of 10 μM) were added, followed by 50 μL of the test compound (appropriate concentration) or buffer. After 15 minutes, incubation at 37°C was terminated by removing the medium and adding 200 μL of 0.1 M HCl. Acid extracts were stored at -20°C until assay. The amounts of cyclic AMP were determined following a protocol which utilized a cAMP binding protein (PKA) [van der Wenden *et al.*, 1995], with the following minor modifications. The assay buffer consisted of 150 mM K_2HPO_4/10 mM EDTA/ 0.2% BSA FV at pH 7.5. Samples (20 mL) were incubated for 90 minutes at 0°C. Incubates were filtered over GF/C glass microfiber filters in a Brandel M-24 Cell Harvester. The filters were additionally rinsed with 4 times

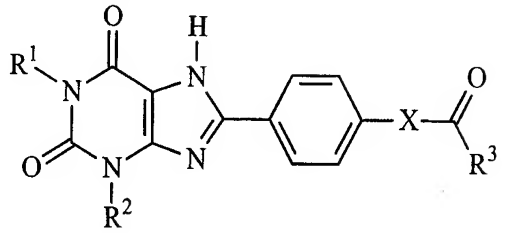
2 mL 150 mM K_2HPO_4/ 10 mM EDTA (pH 7.5, 4°C). Punched filters were counted in Packard Emulsifier Safe scintillation fluid after 2 hours of extraction.

The data from the affinity testing for the compounds of the invention are reported in Tables 1, 2, 3 and 4. The data are reported as Ki in nM or % displacement of specific binding at the designated concentration (where "r" indicates rat cell receptors and "h" indicates human cell receptors).

The data reported for the A_1 term indicates the level of displacement of specific [^{3}H]*R*-PIA binding in rat brain membranes (rA_1) or recombinant human A_1 receptors (hA_1) in HEK 293 cells, expressed as $K_i \pm$ S.E.M. (n = 3-5). The data reported for the A_{2A} term is the level of displacement of specific [^{3}H]CGS 21680 binding in rat striatal membranes (rA_{2A}) or recombinant human A_{2A} receptors (hA_{2A}) in HEK 293 cells, expressed as $K_i \pm$ S.E.M. (n = 3-5). The data reported for the A_{2B} term is the level of displacement of specific [^{125}I]ABOPX binding at human A_{2B} receptors (hA_{2B}) expressed in HEK-293 cells, expressed as $K_i \pm$ S.E.M. (n = 3-4). The A_3 term is the level of displacement of specific [^{125}I]ABA binding at human A_3 receptors (hA_3) expressed in HEK-293 cells, in membranes, expressed as $K_i \pm$ S.E.M. (n = 3-4).

In Table 4 the data reported for the A_{2A} term is the level of displacement of specific [^{3}H]CGS 21680 binding to rat striatal membranes (rA_{2A}) or [^{125}I]ABOPX binding to recombinant human A_{2B} receptors (hA_{2B}) in HEK 293 cells, expressed as $K_i \pm$ S.E.M. in μm (n = 3-6) or as a percentage of specific binding displaced by a solution of test compound, at the the designated concentration. In Table 4 the data reported for the hA_3 term is the level of displacement of specific [^{125}I]AB-MECA binding at human A_3 receptors expressed in HEK-293 cells, in membranes, expressed as $K_i \pm$ S.E.M. in μM (n = 3-4).

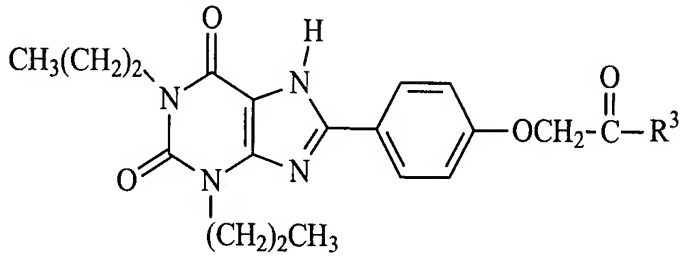
Table 1. Affinities or antagonistic activities of xanthine derivatives in radioligand binding assays at A_1, A_{2A}, A_{2B} and A_3 receptors.



				K_i or IC_{50} (nM)						
Compound	R^1, R^2	X	R^3	rA_1	rA_{2A}	hA_{2B}	hA_3	hA_1/hA_{2B}	hA_{2A}/hA_{2B}	hA_3/hA_{2B}
4a	n-Pr	OCH_2	OH	58 175 ± 57(h)	2,200 595 ± 128(h)	40 ± 4	3,910 ± 2,140 75,700 ± 6,500(r)	4.4	15	98
4b	n-Pr	OCH_2	O-Succinimide	153	127	9.75 ± 4.80	227			
4c	n-Pr	OCH_2	NHN-dimethylmaleiyl	11.1±2.4 3,030 ± 1,110(h)	126±41 1,970 ± 550(h)	26.6 ± 4.0	670 ± 154	110	74	25
4d	n-Pr	OCH_2	$NH(CH_2)_2NH_2$	1.2 6.82 ± 1.57(h)	63 18.4 ± 0.03(h)	7.75 ± 0.14	25.6 ± 5.0	0.9	2.4	3.3
5	allyl	OCH_2	OH	756 ± 147 1,660 ± 580(h)	4,290 ± 570 2,370 ± 290(h)	141 ± 29(h)	816 ± 91 173,000 ± 18,000(r)	12	17	5.8
6	n-butyl	OCH_2	OH	43.1 ± 9.9 149 ± 83(h)	874 ± 107 2,540 ± 1,250(h)	48.0 ± 16.9	90.3 ± 14.2 27,500 ± 2,500(r)	3.1	53	1.9
7	Bn	OCH_2	OH	679 ± 190	25 ± 3% (100,000 nM)[a]	1,760 ± 110				
8	n-Pr	CH=CH	OH	15 140 ± 3 (h)	800 190 ± 71 (h)	60 ± 2	30 ± 14 15,000±1,700(r)	2.3	3.2	0.5
9	c-HexylCH$_2$	CH=CH	OH	602 ± 24 4,890 ± 530(h)	< 10% (10,000nM)[a] 1,518 ± 980(h)	199 ± 52	922 ± 399	25	7.6	4.6
10	Bn	CH=CH	OH	201 ± 23	4,450 ± 1,230	469 ± 23				
71	CH-CH=CH$_2$	OCH_2	NH-Ph(4-CN)	61,200 ± 43,000	4,230 ± 340	9.53 ± 1.9	2680 ± 1810			

a) % Displacement of specific binding at the the designated concentration of test compound.

Table 2. Affinities or antagonistic activities of xanthine amide derivatives in radioligand binding assays[a] at A_1, A_{2A}, A_{2B} and A_3 receptors.

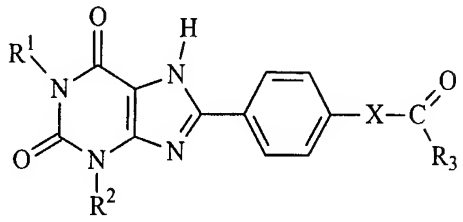


		K_i or IC_{50} (nM)								
Compound	R^3	rA_1	rA_{2A}	hA_1	hA_{2A}	hA_{2B}	hA_3	hA_3/hA_{2B}	hA_1/hA_{2B}	hA_{2A}/hA_{2B}
11	NH_2	20.0 ± 3.8	76.3 ± 14.0			16.3 ± 4.2				
12	NH-Ph	4.22 ± 0.88	45.6 ± 1.4	40.1 ± 5.1	25.8 ± 4.5	1.48 ± 0.63	137 ± 54	27	17	93
13	NH-CH_2Ph	5.02 ± 0.55	25.9 ± 7.6	54.7 ± 21.2	23.8 ± 5.71	2.04 ± 0.17	79.2 ± 17.8	27	12	39
14	NH-$CH(Ph)_2$	120 ± 21	20 ± 8% (1000)[b]			33.7 ± 17.0				
15	$N(CH_2Ph)_2$	167 ± 49	2,750 ± 800	690 ± 98	642 ± 198	9.88 ± 1.05	284 ± 14	70	65	29
16	$N(CH_3)Ph$	218 ± 80	497 ± 250			5.42 ± 1.71				
17	$N(CH_2COOEt)_2$	26.8 ± 2.4	999 ±144			43.4 ± 8.4				
18	NH-Ph-(2-$COCH_3$)	27.9 ± 1.6	434 ± 129	335 ± 64	431±176	2.74 ± 1.01	61.9 ± 3.4	120	160	23
19	NH-Ph-(3-$COCH_3$)	439 ± 111	949 ± 394	234 ± 28	58.9 ± 7.1	4.92 ± 0.55	352 ± 69	48	12	72
20	NH-Ph-(4-$COCH_3$)	37.6 ± 4.0	548 ± 183	157 ± 8	112 ± 37	1.39 ± 0.30	230 ± 23	110	81	170
21	NH-Ph-(4-$COOCH_3$)	38.4 ± 3.9	541 ± 128	225 ± 9	3,100 ± 1540	3.93 ± 1.35	363 ± 148	57	790	92
22	NH-Ph-(4-$CONH_2$)	10.2 ± 2.5	683 ± 167			7.75 ± 1.11				
23	NH-Ph-(4-$CONHCH_3$)	24.8 ± 1.8	98.1 ± 49.6			3.34 ± 0.51				
24	NH-Ph-(4-COOH)	145 ± 28	220 ± 79			16.1 ± 4.7				

		K_i or IC_{50} (nM)								
Compound	R^3	rA_1	rA_{2A}	hA_1	hA_{2A}	hA_{2B}	hA_3	hA_3/hA_{2B}	hA_1/hA_{2B}	hA_{2A}/hA_{2B}
25	NH-Ph-(4-CH_3)	17.5 ± 5.0	126 ± 38			1.88 ± 0.76				
26	NH-Ph-(4-OH)	5.88 ± 1.06	63.3 ± 20.4			3.71 ± 0.76				
27	NH-Ph-(4-CN)	16.8 ± 3.6	612 ± 287	403 ± 194	503 ± 10.8	1.97 ± 0.31	570 ± 184	210	260	290
28	NH-Ph-(4-NO_2)	13.1 ± 3.9	1,180 ± 360	57.0 ± 3.1	70.0 ± 10.7	1.52 ± 0.24	138 ± 17.1	38	46	91
29	NH-Ph-(4-CF_3)	44.6 ± 6.5	917 ± 258	61.2 ± 8.2	238 ± 28	2.14 ± 0.47	213 ± 94	29	110	100
30	NH-Ph-(4-F)	2.72 ± 0.51	988 ± 518	17.9 ± 4.5	16.6 ± 3.6	2.22 ± 0.19	391 ± 147	8.1	7.5	176
31	NH-Ph-(4-Cl)	6.35 ± 1.47	995 ± 550	49.7 ± 14.2	187 ± 38	2.47 ± 0.71	1,870 ± 370	20	400	760
32	NH-Ph-(4-Br)	7.46 ± 2.66	221 ± 36	73.5 ± 23.3	1,640 ± 660	2.35 ± 0.01	2,300 ± 420	31	700	980
33	NH-Ph-(4-I)	15.7 ± 4.2	152 ± 47	293 ± 67	5,140 ± 540	2.13 ± 0.12	1,270 ± 130	140	2,400	600

a) The methods of each binding assay are described above.

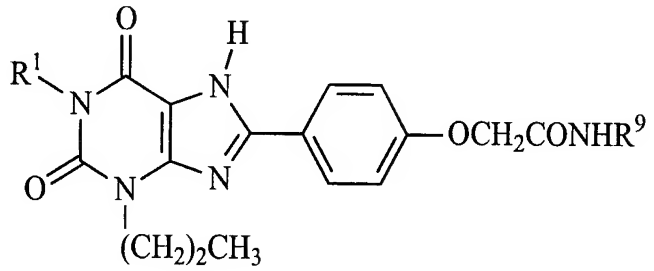
Table 3. Affinities or antagonistic activities of miscellaneous xanthine derivatives in radioligand binding assays[a] at A_1, A_{2A}, A_{2B} and A_3 receptors.

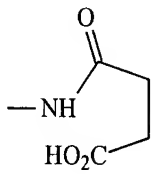


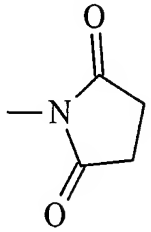
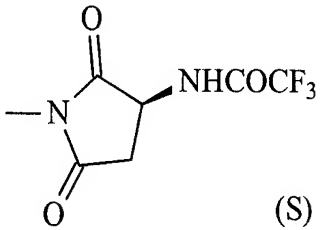
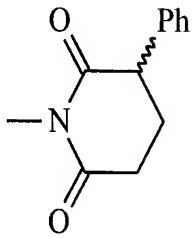
				K_i or IC_{50} (nM)			
Compound	R^1, R^2	X	R^3	rA_1	rA_{2A}	hA_{2B}	hA_3
34	n-Pr	CH=CH	NHN-dimethylmalelyl	3.94 ± 1.20	406 ± 105	16.7 ± 3.0	31.0 ± 3.1
35	n-Pr	CH=CH	NH-Ph-(2-$COCH_3$)	105 ± 5(h) 7.67 ± 2.20	223 ± 55 (h) 143 ± 50	3.65 ± 0.98	121 ± 138
36	c-HexMe	CH=CH	NH-Ph-(2-$COCH_3$)	(10,000 nM)[b]	(10,000 nM)[b]	(10,000 nM)[b]	
37	Bn	CH=CH	NH-Ph-(2-$COCH_3$)	34,300	(10,000 nM)[b]	(10,000 nM)[b]	
38	Bn	OCH_2	NH-Ph-(2-$COCH_3$)	(10,000 nM)[b]	(10,000 nM)[b]	(10,000 nM)[b]	
39	Et	OCH_2	NH-Ph-(4-CH_3)	34.9 ± 0.3	71.1 ± 7.7	1.78 ± 0.43	(1000 nM)[b]
40	Et	OCH_2	NH-Ph-(4-CH_2CONH-$(CH_2)_2NH_2$)	65.0 ± 15.4	1370 ± 490	15.2 ± 6.8	

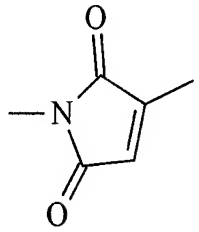
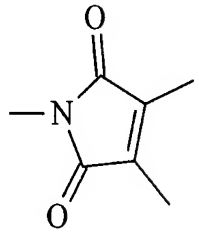
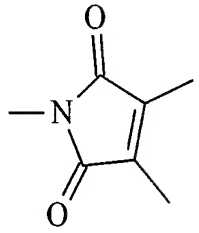
a) The methods of each binding assay are as described above.
b) <10% displacement of specific binding at the the designated concentration of test compound.

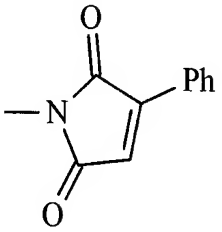
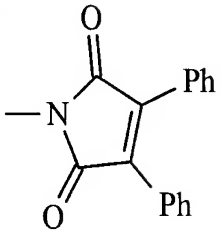
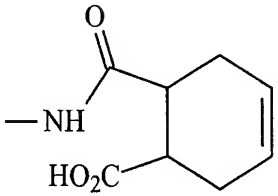
Table 4. Affinities of xanthine derivatives in radioligand binding assays[b] at rat A_1, rat A_{2A}, human A_{2B}, and human A_3 receptors, unless noted[a].

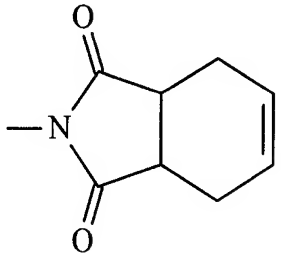
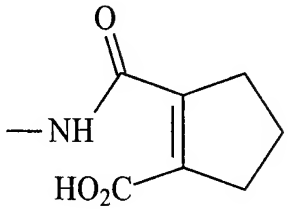
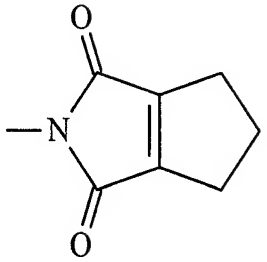


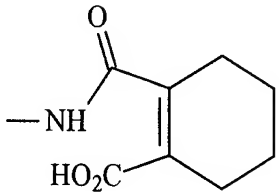
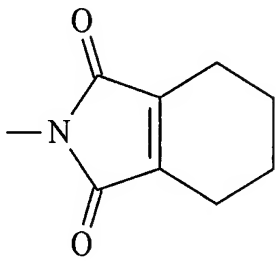
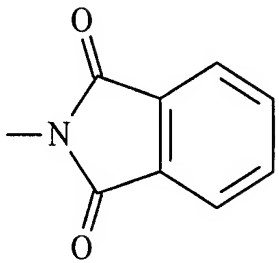
Compound	R^9	R^1	Ki (nM) or % displacement				
			rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
4e	–	Pr	51.6 ± 8.0, 230 ± 59 (h)[a]	128 ± 15, 342 ± 10 (h)[a]	18.7 ± 0.5, 34.5 ± 6.3[a]	48.5 ± 0.8[a]	2.8
4f	$-NH_2$	Pr	16.0 ± 0.5	63.8 ± 21.3	13.2 ± 5.9	498 ± 139	1.2
41	$-NH\text{-}COCH_3$	Pr	6.51 ± 1.24, 125 ± 14 (h)[a]	227 ± 64, 186 ± 9 (h)[a]	65.4 ± 6.5, 33.8 ± 13.7[a]	30.9 ± 8.2[a]	0.10
42		Pr	73.3 ± 22.0, 219 ± 3 (h)[a]	174 ± 32, 795 ± 98 (h)[a]	116 ± 10, 97.8 ± 3.3[a]	173 ± 27	1.6

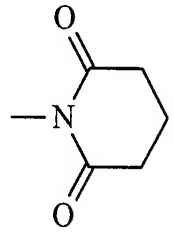
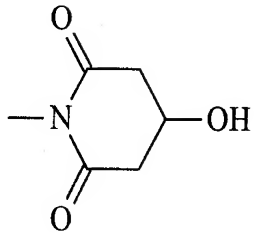
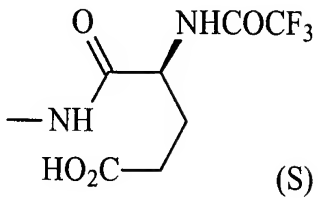
Compound	R^9	R^1	Ki (nM) or % displacement				
			rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
43		Pr	55.9 ± 25.1 75.2 ± 5.5 (h)[a]	805 ± 44 27.2 ± 8.6 (h)[a]	18.6 ± 6.1	766 ± 176	3.0
44	 (S)	Pr	74.3 ± 6.6	139 ± 32	30.2 ± 0.5	1560	2.5
45		Pr	3.87 ± 1.20	21.4 ± 6.1	3.86 ± 0.7	151 ± 99	1.0

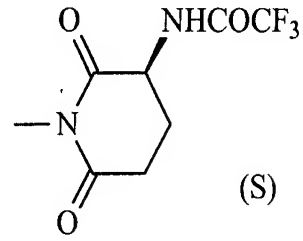
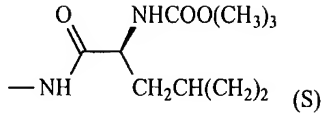
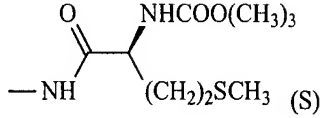
Compound	R^9	R^1	Ki (nM) or % displacement				
			rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
46		Pr	203 ± 41	1230 ± 270	144 ± 11	551 ± 106	1.4
47		Pr	11.1 ± 2.4, 3030 ± 1110 (h)[a]	126 ± 41, 1970 ± 550 (h)[a]	19.4 ± 6.2, 33.8 ± 1.9[a]	670 ± 154[a]	0.57
48		H	3590 ± 920, 8080 ± 720 (h)[a]	36 ± 4% (100,000 nM)[c], 5480 ± 920 (h)[a]	1800 ± 0, 1900 ± 280[a]	14,200 ± 11,500[a]	2.0

Compound	R^9	R^1	Ki (nM) or % displacement				
			rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
49		Pr	225 ± 76	1540 ± 280	66.7 ± 37.0	748 ± 234	3.4
50		Pr	95.8 ± 25. 1	2100 ± 630	27.9 ± 8.5	3450 ± 1470	3.4
51		Pr	134 ± 19	813 ± 299	51.0 ± 7.0	1060 ± 150	2.6

Compound	R^9	R^1	Ki (nM) or % displacement				
			rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
52		Pr	36.4 ± 6.2 129 ± 20 (h)[a]	689 ± 477 301 ± 31 (h)[a]	10.0 ± 3.0	370 ± 190	3.6
53		Pr	81.7 ± 31.2	708 ± 169	78.5 ± 20.5	1180 ± 700	1.0
54		Pr	41.3 ± 6.4	1160 ± 337	21.5 ± 1.5	309 ± 88	1.9

Compound	R^9	R^1	Ki (nM) or % displacement				
			rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
55		Pr	47.2 ± 6.8 145 ± 11 (h)[a]	422 ± 136 95.6 ± 16.8 (h)[a]	17.3 ± 6.3	438 ± 109	2.7
56		Pr	61.9 ± 11.3	415 ± 157	35.8 ± 0.7	245 ± 45	1.7
57		Pr	26.3 ± 2.3, 210 ± 42 (h)[a]	392 ± 117, 359 ± 21 (h)[a]	64.4 ± 0.8, 46.4 ± 14.5[a]	147 ± 21[a]	0.41

Compound	R^9	R^1	Ki (nM) or % displacement				
			rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
58		Pr	14.0 ± 2.3	135 ± 39	22.0 ± 5.5	200 ± 45	0.6
59		Pr	41.2 ± 16.6	164 ± 61	25.7 ± 5.5	290 ± 88	1.6
60	 (S)	Pr	70.8 ± 30.9	872 ± 412	24.8 ± 7.3	430 ± 44	2.9

Compound	R^9	R^1	Ki (nM) or % displacement rA_1	rA_{2A}	hA_{2B}	hA_3	rA_1/hA_{2B}
61	 (S)	Pr	53.5 ± 6.5 149 ± 6 (h)[a]	440 ± 106 178 ± 20 (h)[a]	13.0 ± 3.5	726 ± 245	4.1
62	 (S)	Pr	197 ± 67	2750 ± 950	47.5 ± 2.5	195 ± 84	4.1
63	 (S)	Pr	113 ±27	524 ± 285	39.7 ± 13.6	690 ± 570	2.8
64	Cbz-$(Gly)_2$-NH-	Pr	36.0 ± 6.6 200 ± 22 (h)[a]	609 ± 95 830 ± 84 (h)[a]	10.8 ± 5.0	323 ± 47	3.3

a) K_i values were determined in radioligand binding assays at recombinant human A_1 and A_{2A} receptors expressed in HEK-293 cells vs [^{3}H]CPX and [^{125}I]ZM241385, respectively. Affinity of xanthine derivatives at human A_{2B} receptors expressed in HEK-293 cells was determined using [^{125}I]-ABOPX. Affinity at recombinant human A_3 receptors expressed in HEK-293 cells was determined using [^{125}I]ABA.

b) The methods of each binding assay are as described above.

c) % Displacement of specific binding at the the designated concentration of test compound.

The potency of the xanthine derivatives at human A_{2B} receptors was evaluated using two binding assays. Tables 1, 2 and 3 illustrate the results from the anilide compounds. Table 4 illustrates the results from the hydrazide compounds. Figure 2 shows functional inhibiton by anilide compounds. The K_i values of the xanthine derivatives were determined in displacement of binding of two non-selective radioligands 4-(2-[7-amino-2-{furyl}{1,2,4}triazolo{2,3-a}{1,3,5}triazin-5-ylaminoethyl)-phenol ([^{3}H]ZM241385), and ^{125}I-3-(4-amino-3-iodobenzyl)-8-phenyloxyacetate-1-propyl-xanthine (^{125}I-ABOPX), at human A_{2B} receptors stably expressed in HEK-293 cell membranes. The results obtained with these two radioligands were nearly identical. In order to determine selectivity, the xanthines were evaluated using standard binding assays at A_1, A_{2A}, and A_3 receptors. The initial screening utilized rat brain A_1/A_{2A} receptors (with radioligands [^{3}H]*R*-PIA and [^{3}H]CGS21680), and selected compounds were examined at the recombinant human subtypes, using [^{3}H]8-cyclopentyl-1,3-dipropylxanthine ([^{3}H]CPX) (A_1, See Bruns, R.F., *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1987**, *335*, 59-63.) and ^{125}I-4-(2-[7-amino-2-[2-furyl]-[1,2,4]triazolo[2,3-*a*][1,3,5]-triazin-5-yl-amino]-ethyl)phenol (^{125}I-ZM241385) (A_{2A}). Affinity at cloned human A_3 receptors expressed in HEK-293 cells was determined using N^6-(4-amino-3-[^{125}I]iodobenzyl)-adenosine (^{125}I-ABA) or N^6-(4-amino-3-iodobenzyl)-adenosine-5'-*N*-methyluronamide (^{125}I-AB-MECA).

The 8-(4-Phenylacrylic) acid derivatives, **8** - **10**, tended to be more potent at A_1 receptors and less potent at A_{2B} receptors than the 8-(4-carboxymethyl-oxyphenyl) derivatives. The 1,3-dicyclohexylmethyl derivative, **9**, for example, was more selective for A_{2B} receptors. A primary carboxamide, **11**, was more potent than the carboxylic acid, **4a**, at A_1 (3-fold) and A_{2A} (29-fold) receptors, and equipotent at A_{2B} receptors.

The adenosine receptor affinities of aryl, compounds **12** and **18** - **33**, alkyl, compound **17**, and aralkyl, compounds **13** - **16**, amides of **4a** were compared. A benzyl amide, compound **13**, and simple anilides had the highest affinity of binding, in the nanomolar range, to human A_{2B} receptors. Selectivities for the human A_{2B} versus rat A_1 receptors ranged from 1- (compound **30**) to 27-(compound **20**) fold, while comparisons within the same species (human)

generally led to greater selectivities. Anilides substituted in the *p*-position with groups such as nitro, cyano, and acetyl, displayed the highest selectivity. An N-methyl anilide of **4a**, compound **16**, was 40- and 92-fold selective for human A_{2B} receptors versus rat A_1/A_{2A} receptors, thus the N-methylation reduced affinity by 3.7-fold but increased selectivity. An *o*-substituted acetophenone, compound **18** was 120-, 160-, and 23-fold selective for human A_{2B} receptors versus human $A_1/A_{2A}/A_3$ receptors and 10-, and 160-fold selective versus rat A_1/A_{2A} receptors. The *p*-substituted acetophenone, compound **20**, was more potent at A_{2B} receptors than the corresponding *o*- and *m*- isomers. Other highly potent and moderately selective A_{2B} antagonists were a *p*-trifluoromethyl derivative, compound **29** (K_i value 2.14 nM), and a *p*-cyanoanilide, compound **27** (K_i value 1.97 nM), which was highly selective versus the other human subtypes, but only 8.5-fold selective versus rat A_1 receptors. The *p*-cyanoanilide, **27**, was tritiated on the 1,3-dipropyl groups and serves as a selective radio ligand for A_{2B} receptors. A *p*-nitro derivative, compound **28**, bound to human A_{2B} receptors with a K_i of 1.52 nM but was only 35-fold selective versus human A_1 receptors. A *p*-iodo derivative, compound **33** (K_i value 2.13 nM), was 140-, 2400-, and 600-fold selective for human A_{2B} receptors versus human $A_1/A_{2A}/A_3$ receptors. Substitution of the 1,3-dipropyl groups with ethyl, as in compounds **40** and **41**, offered no disadvantage for selectivity, but high affinities were maintained.

The functional effects of several selective A_{2B} antagonists in inhibiting the effects of NECA in HEK-A_{2B} cells were examined (Figure 2). Several selective A_{2B} adenosine receptor antagonists at 100 nM nearly completely inhibited NECA-stimulated calcium mobilization. In comparison, XAC (8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine), which has a K_i value of 12.3 nM in binding to human A_{2B}, (See de Zwart, M.; *et al.*, *Nucleos. Nucleot.* **1998**, *17*, 969-986.) inhibited the NECA-stimulated calcium mobilization effect by about half. Thus, the potency of the xanthines in the functional assay was parallel to results from the binding assay.

The 1,2-dimethylmaleimide derivative, **47**, bound to human A_{2B} receptors with a K_i of 19 nM and proved to be selective vs. human $A_1/A_{2A}/A_3$ receptors by 160-, 100-, and 35-fold, respectively Other potent and selective $_{2B}$

antagonists were a tetrahydrophthaloyl derivative **52** (K_i value 10 nM) and amino acid conjugates of the XCC-hydrazide, *i.e.*, the glutarimide **61** (K_i value 13 nM) and protected dipeptide **64** (K_i value 11 nM). Compound **55** displayed a K_i value of 17 nM. Other derivatives displaying selectivity for A_{2B} receptors, but with less potency (K_i values in nM) were compounds: **44** (30), **49** (67), **50** (28), **60** (25), **62** (48), and **63** (40).

Synthesis and Characterization

Compounds **4a**, **4b**, **4c**, **11**, **25**, and **26** were synthesized as reported in Jacobson, *et al.*, *J. Med. Chem.* **1985**, *28*, 1334-1340. Compound **5**, **6**, **7** and **10** were synthesized as reported in Kim, H. O.; *et al.*, *J. Med. Chem.* **1994**, *37*, 3373-3382. Compound **39** and **40** were synthesized as reported in Jacobson, K. A *et al.*, *J. Med. Chem.* **1987**, *30*, 211-214. *R*-PIA, NECA, XAC, and 2-chloroadenosine were purchased from Research Biochemicals International (Natick, MA). All other agents were purchased from Aldrich (St. Louis, MO).

Proton nuclear magnetic resonance spectroscopy was performed on a Varian GEMINI-300 spectrometer and spectra were taken in DMSO-d_6 or $CDCl_3$. Unless noted, chemical shifts are expressed as ppm downfield from tetramethylsilane or relative ppm from DMSO (2.5 ppm). Chemical-ionization (CI) mass spectrometry was performed with a Finnigan 4600 mass spectrometer, and Electron-impact (EI) mass spectrometry with a VG7070F mass spectrometer at 6 kV for high resolution mass. FAB (fast atom bombardment) mass spectrometry was performed with a JEOL SX102 spectrometer using 6-kV Xe atoms.

Elemental analysis (±0.4% acceptable) was performed by Atlantic Microlab Inc. (Norcross, GA). All melting points were determined with a Unimelt capillary melting point apparatus (Arthur H. Thomas Co., PA) and were uncorrected. All xanthine derivatives were homogeneous as judged using TLC (MK6F silica, 0.25 mm, glass backed, Whatman Inc., Clifton, NJ). All xanthine derivatives tested in binding assays were shown to be homogeneous by TLC (MK6F silica, 0.25 mm, glass backed, Whatman Inc., Clifton, NJ). NMR and mass spectra were shown to be consistent with the assigned structure.

Example 1. General procedure for the preparation of amide derivatives of 8-[4-[[[carboxyl]methyl]oxy]phenyl]-1,3-dipropylxanthine analogs 4a, 7-10 (collectively "XCC")

Method A (Carbodiimide)

A solution of XCC (0.0517 mmole), the desired amine compound (0.103 mmole), EDAC (20 mg, 0.103 mmole), and DMAP (4 mg, 0.032 mmole) in 2 mL of anhydrous DMF/CH_2Cl_2 (1:1 v/v) was stirred at room temperature for 24 hours. The mixture was evaporated to dryness under reduced pressure. The residue was purified by preparative silica gel TLC ($CHCl_3$:MeOH=20:1) and crystallization in MeOH/ether or MeOH/CH_2Cl_2 to afford the desired compounds (**12-14, 18, 36**).

Method B (BOP-Cl)

A solution of XCC (0.0517 mmole), the desired amine compound (0.103 mmole), BOP-Cl (14 mg, 0.0517 mmole), and triethylamine (20 μl, 0.206 mmole) in 2 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 24 hours. The mixture was treated according to the same procedure as Method A for purification of the desired compounds. (**15, 17, 19, 20, 38**)

Method C (Acid Chloride)

A solution of XCC (0.0517 mmole) in 1 mL of thionyl chloride was stirred at 70°C for 4 hours. The excess thionyl chloride was removed with a nitrogen stream. To the residue was added a solution of the desired amine compound (0.103 mmole) in 1 mL of anhydrous pyridine and 1 mL of anhydrous CH_2Cl_2. The mixture was stirred at room temperature for 24 hours. The mixture was subjected to the same procedure as described in Method A for purification of the desired compounds. (**16, 21, 22, 27-35, 37**)

Example 2. General procedure for the preparation of xanthine hydrazide derivatives

The hydrazide of XCC, **4f**, was acylated with a variety of mono- and dicarboxylic acids. Cyclization reactions were carried out for dicarboxylic acids, in two steps using an anhydride, (compound **72**, Figure 4), for acylation, leading to imide (5- or 6-membered ring) derivatives. The final step of ring-closure of **73** to **74** was effected at 50 °C, using excess carbodiimide and 1-hydroxybenzotriazole as catalyst. In some cases, where symmetric dicarboxylic acids were used, it was possible to isolate both the open structure, **73**, and the cyclized imide form, **74**. Pairs of open and cyclized derivatives of symmetric dicarboxylic acids prepared include compounds **51 - 56**. Also, the glutamic acid derivative **60**, was prepared using orthogonal protecting and the corresponding imide, **61**. An 8-phenyl analogue, **48**, of enprofylline was synthesized by standard methods from the asymmetric urea, (Figure 5).

A. Carboxyalkyl amide derivatives

A mixture of compound **4f** (10 mg, 0.025 mmol), and 2 equivalents of anhydride were stirred in 1 mL of DMF for 6-24 hours. The reaction mixture was concentrated to dryness, and the residue was purified on preparative TLC ($CHCl_3$:MeOH=10:1) to afford the corresponding carboxyalkylamide derivative as a white solid with 40-70% yield. (compounds **41, 42, 51, 53, 55**)

B. Cyclic imide derivatives

A mixture of compound **4f** (10 mg, 0.025 mmol), 1.5-2.0 equivalents of anhydride and 1 equivalent of DIPEA were stirred in 1 mL of DMF at room temperature. When the starting material **4f** disappeared, as judged by TLC, a mixture of 2-3 equivalents of HOBt, EDAC, and DIPEA, dissolved in 0.5 mL of DMF, was added. The mixture was stirred at room temperature or at 50°C for 6-24 hours. The reaction mixture was concentrated to dryness, and the residue was purified on preparative TLC ($CHCl_3$:MeOH=10:1) to afford the cyclic imide derivative as a white solid, 40-70% yield. (compounds **43, 44, 45, 46, 47, 48, 49, 50, 52, 54, 56, 57, 58,** and **59**)

C. Coupling with activated N-protected amino acids

A mixture of compound **4f** (10 mg, 0.025 mmol), 1.5-2.0 equivalents of activated (hydroxy- succinimide or 4-nitrophenyl ester) N-protected amino acid and 1 equivalent of DIPEA and DMAP, in 1 mL of DMF, was stirred at 25-50°C for 8-24 hours. The reaction mixture was concentrated to dryness. The residue was purified by preparative TLC ($CHCl_3$:MeOH=10:1) to afford the product as a white solid, 40-70% yield. (compounds **62, 63** and **64**)

Example 3. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-dibenzyl-xanthine (7)

^{1}H NMR (DMSO-d_6) 4.23 (s, 2H, -OCH_2-), 5.10 (s, 2H, -NCH_2-), 5.23 (s, 2H, -NCH_2-), 6.88 (d, 2H, J = 8.8 Hz, Ar), 7.22-7.41 (m, 10H, 2x-Ph), 8.01 (d, 2H, J = 8.8 Hz, Ar).

Example 4. 8-(4-(2-Carboxy-*trans*-vinyl)phenyl)-1,3-dibenzyl-xanthine (10)

^{1}H NMR (DMSO-d_6) 5.12 (s, 2H, -NCH_2-), 5.26 (s, 2H, -NCH_2-), 6.63 (d, 1H, J = 15.6 Hz, -CH=), 7.22-7.43 (m, 10H, 2x-Ph), 7.63 (d, 1H, J = 15.6 Hz, -CH=), 7.84 (d, 2H, J = 8.8 Hz, Ar), 8.17 (d, 2H, J = 8.8 Hz, Ar).

Example 5. 8-[4-[(Phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)-xanthine (12)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.80 (s, 2H, -OCH_2-), 7.06-7.12 (m, 1H, -Ph), 7.14 (d, 2H, J = 8.8 Hz, Ar), 7.33 (t, 2H, J = 7.8 Hz, -Ph), 7.64 (d, 2H, J = 7.8 Hz, -Ph), 8.09 (d, 2H, J = 8.8 Hz, Ar), 10.13 (s, 1H, -NH).

Example 6. 8-[4-[(Benzylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)-xanthine (13)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.36 (d, 2H, J = 5.9 Hz, -NH-CH_2-), 4.80 (s, 2H, -OCH_2-), 7.12 (d, 2H, J = 8.8 Hz, Ar),

7.22-7.34 (m, 5H, -Ph), 8.08 (d, 2H, J = 8.8 Hz, Ar), 8.70 (t, 1H, J = 5.9 Hz, -NH-).

Example 7. 8-[4-[(Diphenylmethylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (14)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.73 (s, 2H, -OCH_2-), 6.20 (d, 1H, J = 8.8 Hz, -NH-CH_2-), 7.08 (d, 2H, J = 8.8 Hz, Ar), 7.23-7.37 (m, 10H, 2x-Ph), 8.07 (d, 2H, J = 8.8 Hz, Ar), 9.06 (d, 1H, J = 8.8 Hz, -NH-).

Example 8. 8-[4-[(Dibenzylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (15)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.52 (s, 2H, -NCH_2-), 4.59 (s, 2H, -NCH_2-), 5.03 (s, 2H, -OCH_2-), 6.99 (d, 2H, J = 8.8 Hz, Ar), 7.22-7.44 (m, 10H, 2x-Ph), 8.05 (d, 2H, J = 8.8 Hz, Ar).

Example 9. 8-[4-[(N-Methyl-N-phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (16)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.22 (s, 3H, -NCH_3), 3.88 and 4.01 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.54 (s, 2H, -OCH_2-), 6.91 (bs, 2H, Ar), 7.30-7.55 (m, 5H, -Ph), 8.03 (d, 2H, J = 8.8 Hz, Ar).

Example 10. 8-[4-[(N,N-bis(ethoxycarbonylmethyl) carbamoylmethyl)-oxy]phenyl]-1,3-di-(n-propyl)xanthine (17)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.20 (2t, 6H, J = 6.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.06-4.20 (m, 4H, -OCH_2-), 4.11 (s, 2H, -NCH_2-), 4.38 (s, 2H, -NCH_2-), 4.94 (s, 2H, -OCH_2-), 7.00 (d, 2H, J = 8.8 Hz, Ar), 8.05 (d, 2H, J = 8.8 Hz, Ar).

Example 11. 8-[4-[((2-Acetylphenyl)carbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (18)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.70 (s, 3H, -$COCH_3$), 4.72 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.56 (t, 1H, J = 6.8 Hz, Ar), 7.69 (t, 1H, J = 6.8 Hz, Ar), 8.02 (d, 2H, J = 6.8 Hz, Ar), 8.11 (d, 2H, J = 8.8 Hz, Ar), 8.48 (m, 1H, -NH-).

Example 12. 8-[4-[((3-Acetylphenyl)carbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (19)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.74 (2m, 4H, 2x-CH_2-), 2.57 (s, 3H, -$COCH_3$), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.82 (s, 2H, -OCH_2-), 7.16 (d, 2H, J = 8.8 Hz, Ar), 7.50 (t, 1H, J = 7.8 Hz, Ar), 7.71 (d, 1H, J = 7.8 Hz, Ar), 7.92 (d, 1H, J = 7.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar), 8.24 (s, 1H, Ar), 10.36 (s, 1H, -NH-).

Example 13. 8-[4-[((4-Acetylphenyl)carbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (20)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 2.54 (s, 3H, -$COCH_3$), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.85 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.79 (d, 2H, J = 7.8 Hz, Ar), 7.96 (d, 2H, J = 7.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar), 10.48 (s, 1H, -NH-).

Example 14. 8-[4-[((4-Methoxycarbonyl)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (21)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.83 (s, 3H, -OCH_3), 3.86 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.85 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 7.79 (d, 2H, J = 7.8 Hz, Ar), 7.96 (d, 2H, J = 7.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar), 10.50 (s, 1H, -NH-).

Example 15. 8-[4-[((4-Carbamoyl)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (22)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.82 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 7.26 (bs, 1H, -NH_2), 7.70 (d, 2H, J = 7.8 Hz, Ar), 7.85 (m, 3H, Ar and –NH_2), 8.10 (d, 2H, J = 8.8 Hz, Ar), 10.35 (s, 1H, -NH-).

Example 16. 8-[4-[((4-Methylcarbamoyl)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (23)

A solution of 20 mg of compound **21** (0.0358 mmole) in 1 mL of 40% aqueous methylamine was stirred at room temperature for 1 hour. The mixture was evaporated to dryness under reduced pressure, and the residue was purified by preparative silica gel TLC ($CHCl_3$:MeOH=20:1) and re-crystallized in MeOH/CH_2Cl_2 to afford 9 mg of compound **23**. ^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.73 (2m, 4H, 2x-CH_2-), 2.76 (s, 3H, -$NHCH_3$), 3.86 and 4.01 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.82 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 7.71 (d, 2H, J = 7.8 Hz, Ar), 7.81 (d, 2H, J = 7.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar), 8.33 (m, 1H, -$NHCH_3$), 10.34 (s, 1H, -NH-).

Example 17. 8-[4-[((4-Carboxy)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (24)

A suspension of 20 mg of compound **21** (0.0385 mmole) in 1 mL of 1 N NaOH solution was stirred for 2 hours to turn to a clear solution. The mixture was neutralized by adding 1 mL of 1 N HCl solution. The precipitate was collected by filtration, and purified by low pressure (C18) column chromatography using linear gradient elution of 1 M triethylammonium acetate buffer (pH=7.0) and CH_3CN (90/10 to 40/60) to afford 10 mg of compound **24**. ^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.01 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.84 (s, 2H, -

OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 7.77 (d, 2H, J = 8.8 Hz, Ar), 7.92 (d, 2H, J = 8.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar), 10.45 (s, 1H, -NH-).

Example 18. 8-[4-[((4-Cyano)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (27)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.86 and 4.01 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.85 (s, 2H, -OCH_2-), 7.13 (d, 2H, J = 8.8 Hz, Ar), 7.80 (d, 2H, J = 7.8 Hz, Ar), 7.84 (d, 2H, J = 7.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar), 10.58 (s, 1H, -NH-).

Example 19. 8-[4-[((4-Nitro)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (28)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.89 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.91 (d, 2H, J = 8.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar), 8.26 (d, 2H, J = 8.8 Hz, Ar), 10.76 (s, 1H, -NH-).

Example 20. 8-[4-[((4-Trifluoromethyl)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (29)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.85 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.71 (d, 2H, J = 7.8 Hz, Ar), 7.87 (d, 2H, J = 7.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar), 10.51 (s, 1H, -NH-).

Example 21. 8-[4-[((4-Fluoro)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (30)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.79 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.19 (d, 2H, J = 8.8 Hz, Ar), 7.66 (dd, 2H, J = 5.9, 8.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar), 10.20 (s, 1H, -NH-).

Example 22. 8-[4-[((4-Chloro)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (31)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.80 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 7.8 Hz, Ar), 7.39 (d, 2H, J = 7.8 Hz, Ar), 7.68 (d, 2H, J = 7.8 Hz, Ar), 8.09 (d, 2H, J = 7.8 Hz, Ar), 10.27 (s, 1H, -NH-).

Example 23. 8-[4-[((4-Bromo)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (32)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.80 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 7.52 (d, 2H, J = 8.8 Hz, Ar), 7.63 (d, 2H, J = 8.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar), 10.27 (s, 1H, -NH-).

Example 24. 8-[4-[((4-Iodo)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (33)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.79 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 7.8 Hz, Ar), 7.49 (d, 2H, J = 7.8 Hz, Ar), 7.68 (d, 2H, J = 7.8 Hz, Ar), 8.09 (d, 2H, J = 7.8 Hz, Ar), 10.24 (s, 1H, -NH-).

Example 25. 8-(4-(2-Carboxy-*trans*-vinyl)phenyl)-1,3-di-(n-propyl)xanthine N',N'-[(1,2-Dimethyl)maleyl]hydrizide (34)

^{1}H NMR ($CDCl_3$). 1.01 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.72 and 1.89 (2m, 4H, 2x-CH_2-), 2.05 (s, 6H, 2x-CH_3), 4.02 and 4.17 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 6.67 (d, 1H, J = 15.6 Hz, -CH=), 7.63 (d, 2H, J = 8.8 Hz, Ar), 7.74 (d, 1H, J = 15.6 Hz, -CH=), 8.09 (d, 2H, J = 8.8 Hz, Ar), 9.43 (s, 1H, -NH-).

Example 26. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-di-(n-propyl)xanthine (35)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.76 (2m, 4H, 2x-CH_2-), 3.88 and 4.04 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.79 (d, 3H, J = 4.9 Hz, -$COCH_3$), 6.93 (d, 1H, J = 15.6 Hz, -CH=), 7.51 (d, 1H, J = 15.6

Hz, -CH=), 7.57 (t, 1H, J = 7.8 Hz, Ar), 7.69 (t, 1H, J = 7.8 Hz, Ar), 7.75 (d, 2H, J = 7.8 Hz, Ar), 8.03 (d, 2H, J = 7.8 Hz, Ar), 8.18 (d, 2H, J = 7.8 Hz, Ar), 8.53 (t, 1H, J = 5.8 Hz, -NH-).

Example 27. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-di-(cyclohexylmethyl)xanthine (36)

^{1}H NMR ($CDCl_3$). 1.02-1.27 (m, 8H, c-Hex.), 1.45-1.72 (m, 14H, c-Hex.), 4.00 and 4.08 (2d, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.96 (d, 3H, J = 3.9 Hz, -$COCH_3$), 6.66 (d, 1H, J = 15.6 Hz, -CH=), 6.86 (bs, 1H, -NH-), 7.54 (t, 2H, J = 7.8 Hz, Ar), 7.64-7.78 (m, 3H, -CH= and Ar), 8.06 (d, 2H, J = 7.8 Hz, Ar), 8.24 (d, 2H, J = 8.8 Hz, Ar).

Example 28. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-dibenzylxanthine (37)

^{1}H NMR (DMSO-d_6) 4.79 (d, 3H, J = 5.8 Hz, -$COCH_3$), 5.13 (s, 2H, -NCH_2-), 5.27 (s, 2H, -NCH_2-), 6.93 (d, 1H, J = 15.6 Hz, -CH=), 7.24-7.41 (m, 10H, 2x-Ph), 7.46 (d, 1H, J = 15.6 Hz, -CH=), 7.57 (t, 1H, J = 8.8 Hz, Ar), 7.69 (t, 1H, J = 7.8 Hz, Ar), 7.75 (d, 2H, J = 8.8 Hz, Ar), 8.03 (d, 2H, J = 7.8 Hz, Ar), 8.20 (d, 2H, J = 7.8 Hz, Ar), 8.54 (t, 1H, J = 5.8 Hz, -NH-).

Example 29. 8-[4-[((2-Acetylphenyl)carbamoylmethyl)oxy]phenyl]-1,3-dibenzyl-xanthine (38)

^{1}H NMR (DMSO-d_6) 4.68 (s, 3H, -$COCH_3$), 4.71 (s, 2H, -OCH_2-), 5.12 (s, 2H, -NCH_2-), 5.26 (s, 2H, -NCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.23-7.42 (m, 10H, 2x-Ph), 7.55 (t, 1H, J = 7.8 Hz, Ar), 7.68 (t, 1H, J = 7.8 Hz, Ar), 8.02 (d, 2H, J = 7.8 Hz, Ar), 8.11 (d, 2H, J = 8.8 Hz, Ar), 8.48 (t, 1H, J = 4.8 Hz, -NH-).

Example 30. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-Acetylhydrazide (41)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 1.88 (s, 3H, CH_3CO-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz,

2x-NCH_2-), 4.68 (s, 2H, -OCH_2-), 7.11 (d, 2H, J = 8.8 Hz, Ar), 8.08 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 443.

Example 31. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-[(3-Carboxy)-*n*-propionyl]hydrazide (42)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 2.43 (m, 4H, -$COCH_2CH_2CO$-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.67 (s, 2H, -OCH_2-), 7.11 (d, 2H, J = 8.8 Hz, Ar), 8.08 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 501.

Example 32. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-Succinylhydrazide (43)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.73 (2m, 4H, 2x-CH_2-), 2.81 (s, 4H, CH_2CH_2), 3.87 and 4.03 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.85 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 483.

Example 33. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-[((2*S*)-Trifluoroacetamido)succinyl]hydrazide (44)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 2.70-2.90 (m, 2H, -CH_2-), 3.81 and 3.98 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.69 (s, 2H, -OCH_2-), 4.95 (s, 1H, -CH-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 594.

Example 34. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-[(2-Phenyl)glutaryl]hydrazide (45)

^{1}H NMR ($CDCl_3$). 1.05 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.75 and 1.90 (2m, 4H, 2x-CH_2-), 2.3-2.5 and 2.8-3.1 (m, 5H, -CH- and 2x-CH_2-), 4.04 and 4.12 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.70-4.90 (m, 2H, -OCH_2-), 6.6 (d, 2H, J = 8.8 Hz, Ar), 7.08 (m, 2H, -Ph), 7.43 (m, 5H, -Ph and Ar); MS-FAB (M + H^+) 573.

Example 35. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-Citraconylhydrazide (46)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.73 (2m, 4H, 2x-CH_2-), 2.07 (s, 3H, CH_3), 3.87 and 4.03 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.86 (s, 2H, -OCH_2-), 6.83 (s, 1H, =CH-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 495.

Example 36. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-[(1,2-Dimethyl)maleyl]hydrazide (47)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 1.97 (s, 6H, 2x-CH_3), 3.87 and 4.03 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.86 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 8.10 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 509.

Example 37. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine *N,N*-[(1,2-Dimethyl)maleyl]hydrazide (48)

^{1}H NMR (DMSO-d_6). 0.91 (t, 3H, J = 7.8 Hz, 2x-CH_3), 1.73 (m, 2H, -CH_2-), 1.97 (s, 6H, 2x-CH_3), 3.96 (t, 2H, J = 6.8 Hz, 2x-NCH_2-), 4.85 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar); MS-EI (M^+) 509, Calcd. for $C_{22}H_{22}N_6O_6$ 466.1601; Found 466.1580.

Example 38. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-[(2-Phenyl)maleyl]hydrazide (49)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.73 (2m, 4H, 2x-CH_2-), 3.87 and 4.03 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.91 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.51 (s, 1H, =CH-), 7.55-7.57 (m, 3H, -Ph), 8.04-8.06 (m, 2H, -Ph), 8.11 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 557.

Example 39. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-[(1,2-Diphenyl)maleyl]hydrazide (50)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.73 (2m, 4H, 2x-CH_2-), 3.87 and 4.03 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.94 (s, 2H,

-OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 7.45 (bs, 10H, 2x-Ph), 8.10 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 633.

Example 40. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-[2-((1-Carboxy)-cis-4-cyclohexene)-carbonyl]hydrazide (51)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 2.30-2.50 (m, 4H, 2x-CH_2-), 2.80-2.95 (m, 2H, 2x-CH-), 3.83 and 3.90 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.66 (s, 2H, -OCH_2-), 5.63 (s, 2H, 2 x =CH-), 7.09 (d, 2H, J = 8.8 Hz, Ar), 8.06 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 553.

Example 41. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(*cis*-1,2,3,6-Tetrahydrophthaloyl)hydrazide (52)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 2.20-2.50 (m, 4H, 2x-CH_2-), 3.56 (m, 2H, 2x-CH-), 3.83 and 3.90 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.66 (s, 2H, -OCH_2-), 5.89 (s, 2H, 2 x =CH-), 7.09 (d, 2H, J = 8.8 Hz, Ar), 8.06 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 535.

Example 42. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-[2-((1-Carboxy)-1-cyclopentene)-carbonyl]hydrazide (53)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 1.87 (m, 2H, -CH_2-), 2.70 (m, 4H, 2x-CH_2-), 3.83 and 3.90 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.71 (s, 2H, -OCH_2-), 7.09 (d, 2H, J = 8.8 Hz, Ar), 8.06 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 539.

Example 43. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(1-Cyclopentene-1,2-dicarbonyl)hydrazide (54)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 2.40 (m, 2H, -CH_2-), 2.67(4H, m, 2x-CH_2-), 3.81 and 3.98 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.85 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 8.1 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 521.

Example 44. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-[2-((1-Carboxy)-1-cyclohexene)-carbonyl]hydrazide (55)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 (m, 6H, 3x-CH_2-), 1.74 (m, 2H, -CH_2-), 2.27 (m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.68 (s, 2H, -OCH_2-), 7.09 (d, 2H, J = 8.8 Hz, Ar), 8.06 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 553.

Example 45. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(3,4,5,6-Tetrahydrophthaloyl)hydrazide (56)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 (m, 2H, -CH_2-), 1.72 (m, 6H, 3x-CH_2-), 2.30 (m, 4H, 2x-CH_2-) 3.83 and 3.90 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.86 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 8.12 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 535.

Example 46. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-Phthaloylhydrazide (57)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.75 (s, 2H, -OCH_2-), 7.14 (d, 2H, J = 8.8 Hz, Ar), 7.57 (m, 4H, Ar), 8.09 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 531

Example 47. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-Glutarylhydrazide (58)

^{1}H NMR ($CDCl_3$). 1.05 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.75 and 1.90 (2m, 4H, 2x-CH_2-), 2.10-2.30 (m, 2H, -CH_2-), 2.80-3.10 (m, 4H, 2x-CH_2-), 4.05 and 4.16 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.80 (s, 2H, -OCH_2-), 6.75 (d, 2H, J = 8.8 Hz, Ar), 7.70 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 497.

Example 48. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-(3-Hydroxy)glutarylhydrazide (59)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.73 (2m, 4H, 2x-CH_2-), 2.70-3.10 (m, 4H, 2x-CH_2-), 3.87 and 4.03 (2t, 4H, J = 6.8

Hz, -NCH_2-), 4.21 (bs, 1H, -CHOH-), 4.77 (s, 2H, -OCH_2-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 8.1 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 513.

Example 49. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-[(4-Carboxy-(2*S*)-Trifluoroacetamido)-*n*-butanoyl]hydrazide (60)

A mixture of compound **4f** (10 mg, 0.025 mmol), 7.6 mg of L-N-Boc-glutamic acid 5-*tert*-butyl ester (0.025 mmole), 7 mg of HOBt (0.05 mmole), 19 mg of DIPEA (0.15 mmole) and 15 mg of EDAC (0.078 mmole) in 1 mL of dry DMF was stirred for 8 hours at 25°C. The DMF was removed by nitrogen stream. The residue was washed with 1 mL of 1 M $NaHCO_3$ solution and dried overnight. The crude product was suspended in 0.5 mL of $CHCl_3$ and 0.5 mL of TFA added. After stirring for 30 minutes at 25°C, the mixture was concentrated to dryness and dried under high vacuum. The residue was dissolved in 0.5 mL of TFAA and the solution was stirred for 30 minutes at 25°C. The reaction mixture was concentrated to dryness, and the residue was purified by preparative TLC ($CHCl_3$:MeOH=10:1) to afford 6 mg of compound **60** as a white solid (yield 40%). ^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.73 (2m, 4H, -CH_2-), 1.90-2.30 (m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.12 (m, 1H, -CH-), 4.68 (s, 2H, -OCH_2-), 7.08 (d, 2H, J = 8.8 Hz, Ar), 8.06 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M+ H^+) 626.

Example 50. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N,N*-((2*S*)-Trifluoroacetamido)glutaryl]hydrazide (61)

A mixture of compound **60** (10 mg, 0.016 mmol), 7 mg of HOBt (0.05 mmole), 19 mg of DIPEA (0.15 mmole) and 15 mg of EDAC (0.078 mmole) in 1 mL of dry DMF was stirred overnight at 25°C. The reaction mixture was concentrated to dryness, and the residue was purified by preparative TLC ($CHCl_3$:MeOH=10:1) to afford 5 mg of compound **61** as a white solid (yield 53%). ^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.59 and 1.73 (2m, 4H, 2x-CH_2-), 1.90-2.30 (m, 4H, 2x-CH_2-), 3.87 and 4.02 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.81 (s, 2H, -OCH_2-), 4.18 (m, 1H, -CH-), 7.15 (d, 2H, J = 8.8 Hz, Ar), 8.1 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 608.

Example 51. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-(*N*-*tert*-Butoxycarbonyl-L-leucinyl)hydrazide 62)

^{1}H NMR (DMSO-d_6). 0.89 (m, 13H, 2x-CH_3 and $(CH_3)_2CH$-), 1.35 (s, 9H, Boc), 1.42 (m, 2H, -CH_2-), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.85 and 4.0 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.12 (m, 1H, -CH-), 4.64 (s, 2H, -OCH_2-), 7.06 (d, 2H, J = 8.8 Hz, Ar), 8.05 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 614.

Example 52. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-(*N*-*tert*-Butoxycarbonyl-L-methionyl)hydrazide (63)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.25 (m, 2H, -CH_2-), 1.37 (s, 9H, Boc), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 1.88 (m, 2H, -CH_2-), 2.03 (s, 3H, -SCH_3), 3.81 and 3.98 (2t, 4H, J = 6.8 Hz, 2x-NCH_2-), 4.15 (m, 1H, -CH-), 4.68 (s, 2H, -OCH_2-), 7.03 (d, 2H, J = 8.8 Hz, Ar), 8.03 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 632.

Example 53. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-(*N*-Benzyloxycarbonyl-glycylglycinyl)hydrazide (64)

^{1}H NMR (DMSO-d_6). 0.89 (2t, 6H, J = 7.8 Hz, 2x-CH_3), 1.58 and 1.74 (2m, 4H, 2x-CH_2-), 3.67 (m, 1H, -CH_2- in glycine), 3.81 (m, 3H, -NCH_2- and -CH_2- in glycine), 3.98 (t, 2H, J = 6.8 Hz, -NCH_2-), 4.64 (s, 2H, -OCH_2-), 5.03(s, 2H, -OCH_2-Ph), 7.03 (d, 2H, J = 8.8 Hz, Ar), 7.3-7.5 (m, 5H, -Ph), 8.03 (d, 2H, J = 8.8 Hz, Ar); MS-FAB (M + H^+) 649.

Example 54. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine Methyl Ester (65)

To a suspension of 3.2 g of 2,5-dioxo-4-amino-3-propyl tetrahydro pyrimidine, **66** [prepared according to the method described in Papesch *et al.*, J. Org. Chem., 16, 1879-1890 (1951)] (18.9 mmole), 1.5 mL of glacial acetic acid and 3.4 mL of 6 N HCl in 50 mL of water was added dropwise a solution of 1.38 g of sodium nitrite (20 mmole) in 5 mL of water at 0°C. The mixture was stirred for 1 hour and the pink precipitate was collected by filtration to afford 3.17 g of nitro-amine, **67** (yield 78%). ^{1}H NMR (DMSO-d_6) 0.87 (t, 3H,

J = 7.8 Hz, -CH_3), 1.51 (m, 2H, -CH_2-), 3.72 (t, 2H, J = 6.8 Hz, -NCH_2-), 9.12 (s, 1H, -NH_2).

0.086 g of nitro-amine, **67** (0.4 mmole) was hydrogenated with 10% Pd/C in 5 mL of MeOH under H_2 atmosphere (1 atm) at 25°C until the pink color disappeared (30 min). After the removal of the balloon of H_2, 5 mL of DMF was added and the mixture was stirred for 10 min and filtered through a Celite bed.

To the solution of crude diamine, **68** was added 0.078 g of methyl 4-formylphenyloxyacetate (0.4 mmole) and 0.5 mL of acetic acid. The mixture was heated at 50°C for 30 min, evaporated under reduced pressure and suspended in 20 mL of ether. The yellow precipitate (mixture of **69** and **65**) was collected by filtration, dissolved in 5 mL of DMF and treated with 1 mL of aqueous solution of 0.085 g of sodium periodate (0.4 mmole) for 2 hours. After evaporation, the product was purified by crystallization in MeOH/H_2O to afford 0.048 g of xanthine, **65** (yield 34%). ^{1}H NMR (DMSO-d_6). 0.90 (t, 3H, J = 7.8 Hz, -CH_3), 1.72 (m, 2H, -CH_2-), 3.71 (s, 3H, -OCH_3), 3.95 (t, 2H, J = 6.8 Hz, -NCH_2-), 4.89 (s, 2H, -OCH_2-), 7.08 (d, 2H, J = 8.8 Hz, Ar), 8.05 (d, 2H, J = 8.8 Hz, Ar), 11.07 (s, 1H, -NH); MS-EI (M^+) 358, Calcd. for $C_{17}H_{18}N_4O_5$ 358.1277; Found 358.1269.

Example 55. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine Hydrazide (70)

A solution of 0.05 g of xanthine **65** (0.14 mmole) and 0.5 mL of hydrazine anhydrous in 2 mL of dry DMF was heated overnight at 50°C. After evaporation, the residue was suspended in MeOH and the white precipitate was collected by filtration to give 0.025 g of **70** (yield 50%). m.p. = 267°C; ^{1}H NMR (DMSO-d_6). 0.90 (t, 3H, J = 7.8 Hz, -CH_3), 1.72 (m, 2H, -CH_2-), 3.71 (s, 3H, -OCH_3), 3.95 (t, 2H, J = 6.8 Hz, -NCH_2-), 4.34 (bs, 2H, NH_2), 4.56 (s, 2H, -OCH_2-), 7.08 (d, 2H, J = 8.8 Hz, Ar), 8.05 (d, 2H, J = 8.8 Hz, Ar), 9.39 (s, 1H, -NH); MS-EI (M^+) 358, Calcd. for $C_{16}H_{18}N_6O_4$ 358.1389; Found 358.1389.

Table 5 contains data for yields and characterization of the xanthine compounds of the invention. Table 6 contains data for elemental analysis of the xanthine compounds of the invention.

Table 5. The yields and chemical characterization of xanthine derivatives.

Compound	%yield	m.p.(°C)	MS	Formula	Analysis
7	13	>310	EI:482	$C_{27}H_{22}N_4O_5$	HRMS[a]
10	40	>310	FAB:479	$C_{28}H_{22}N_4O_4$	C,H,N
12	71	301-302	CI:462	$C_{25}H_{27}N_5O_4$	C,H,N
13	41	268	CI:476	$C_{26}H_{29}N_5O_4$	C,H,N
14	46	269-270	EI:551	$C_{32}H_{33}N_5O_4$	C,H,N
15	55	230	EI:565	$C_{33}H_{35}N_5O_4$	C,H,N
16	49	215	FAB:476	$C_{26}H_{29}N_5O_4$	C,H,N
17	13	225	CI:558	$C_{27}H_{35}N_5O_8$	C,H,N
18	68	294	EI:503	$C_{27}H_{29}N_5O_5$	C,H,N
19	29	269-270	EI:503	$C_{27}H_{29}N_5O_5$	HRMS[a]
20	29	309-310	EI:503	$C_{27}H_{29}N_5O_5 \cdot 0.23H_2O$	C,H,N
21	56	>310	CI:520	$C_{27}H_{29}N_5O_6$	C,H,N
22	19	>310	CI:505	$C_{26}H_{28}N_6O_5$	C,H,N
23	45	>310	FAB:519	$C_{27}H_{30}N_6O_5 \cdot 1.8CH_2Cl_2$	C,H,N
24	51	>310	FAB:506	$C_{26}H_{27}N_5O_6 \cdot 0.60CH_2Cl_2$	C,H,N
27	44	>310	CI:487	$C_{26}H_{26}N_6O_4$	C,H,N
28	31	307	CI:507	$C_{25}H_{26}N_6O_6 \cdot 0.43CH_3OH$	C,H,N
29	44	>310	CI:530	$C_{26}H_{26}F_3N_5O_4 \cdot 0.26CH_3OH$	C,H,N
30	48	298	CI:480	$C_{25}H_{26}FN_5O_4$	C,H,N
31	31	309	CI:496	$C_{25}H_{26}ClN_5O_4 \cdot 0.26(CH_3)_2CO$	C,H,N
32	36	>310	CI:540	$C_{25}H_{26}BrN_5O_4$	C,H,N
33	13	>310	CI:588	$C_{25}H_{26}IN_5O_4 \cdot 0.60CH_3OH$	C,H,N
4c	79	>310	FAB:509	$C_{25}H_{28}N_6O_6$	C,H,N
34	49	302-303	EI:504	$C_{26}H_{28}N_6O_5$	C,H,N
35	42	281-283	CI:500	$C_{28}H_{29}N_5O_4 \cdot 0.27MeOH$	C,H,N
36	33	305	FAB:608	$C_{36}H_{41}N_5O_4$	HRMS[a]
37	76	308-309	CI:596	$C_{36}H_{29}N_5O_4 \cdot 0.60H_2O$	C,H,N
38	18	284	EI:599	$C_{35}H_{29}N_5O_5$	HRMS[a]

a) High-resolution mass in EI or FAB^+ mode (*m/z*) determined to be within acceptable limits: **7**: calcd, 482.1590; found, 482.1597, **19**: calcd, 503.2169; found, 503.2169, **36**: calcd, 608.3237; found, 608.3251; **38**: calcd, 599.2169; found, 599.2171.

Table 6. Elemental Analysis of Xanthine Derivatives

Compound No.	Formula	MW (anhyd)	Calculated (% or HRMS)	Found (% or HRMS)
7	$C_{27}H_{22}N_4O_5$	482.49	482.1590	482.1597
10	$C_{28}H_{22}N_4O_4$	478.50	C70.28, H4.63, N11.70	C70.16, H4.72, N11.72
12	$C_{25}H_{27}N_5O_4$	461.52	C65.06, H5.90, N 15.17	C65.04, H5.93, N15.20
13	$C_{26}H_{29}N_5O_4$	475.54	C65.66, H6.15, N14.72	C65.70, H6.22, N14.72
14	$C_{32}H_{33}N_5O_4$	551.64	C69.67, H6.03, N12.69	C69.60, H6.08, N12.66
15	$C_{33}H_{35}N_5O_4$	565.67	C70.06, H6.24, N12.38	C70.01, H6.33, N12.35
16	$C_{26}H_{29}N_5O_4$	475.54	C65.66, H6.15, N14.72	C65.45, H6.23, N14.68
17	$C_{27}H_{35}N_5O_8$	557.60	C58.15, H6.33, N12.56	C57.93, H6.38, N12.41
18	$C_{27}H_{29}N_5O_5$	503.55	C64.40, H5.81, N13.90	C64.24, H5.83, N13.87
19	$C_{27}H_{29}N_5O_5$	503.55	503.2169	503.2169
20	$C_{27}H_{29}N_5O_5$	503.55	C64.40, H5.81, N13.90	
	$C_{27}H_{29}N_5O_5 \cdot 0.23H_2O$	507.70	C63.88, H5.85, N13.79	C63.74, H5.77, N13.80
21	$C_{27}H_{29}N_5O_6$	519.55	C62.41, H5.63, N13.48	C62.58, H5.67, N13.36
22	$C_{26}H_{28}N_6O_5$	504.54	C61.89, H5.59, N16.65	C60.64, H5.66, N15.58
23	$C_{27}H_{30}N_6O_5$	518.57	C62.53, H5.83, N16.20	
	$C_{27}H_{30}N_6O_5 \cdot 1.80CH_2Cl_2$	671.45	C51.51, H5.04, N12.51	C51.75, H4.92, N12.77
24	$C_{26}H_{27}N_5O_6$	505.53	C61.77, H5.38, N13.85	
	$C_{26}H_{27}N_5O_6 \cdot 0.60CH_2Cl_2$	556.49	C57.41, H5.11, N12.58	C57.12, H5.18, N12.46
27	$C_{26}H_{26}N_6O_4$	486.53	C64.18, H5.39, N17.27	C64.27, H5.47, N17.03
28	$C_{25}H_{26}N_6O_6$	506.51	C59.28, H5.17, N16.59	
	$C_{25}H_{26}N_6O_6 \cdot 0.43CH_3OH$	520.30	C58.70, H5.37, N16.15	C58.63, H5.26, N15.98
29	$C_{26}H_{26}F_3N_5O_4$	529.51	C58.97, H4.95, N13.22	
	$C_{26}H_{26}F_3N_5O_4 \cdot 0.26CH_3OH$	537.85	C58.64, H5.07, N13.02	C58.74, H5.07, N12.96
30	$C_{25}H_{26}FN_5O_4$	479.51	C62.62, H5.47, N14.60	C62.39, H5.49, N14.31
31	$C_{25}H_{26}ClN_5O_4$	495.96	C60.54, H5.28, N14.12	
	$C_{25}H_{26}ClN_5O_4 \cdot 0.26(CH_3)_2CO$	511.07	C60.59, H5.44, N13.70	C60.59, H5.40, N13.62
32	$C_{25}H_{26}BrN_5O_4$	540.41	C55.56, H4.85, N12.95	C55.28, N4.89, N12.70
33	$C_{25}H_{26}IN_5O_4$	587.41	C51.11, H4.46, N11.92	
	$C_{25}H_{26}IN_5O_4 \cdot 0.60CH_3OH$	606.64	C50.68, H4.72, N11.54	C50.48, H4.40, N11.28
4c	$C_{25}H_{28}N_6O_6$	508.53	C59.04, H5.55, N16.52	C58.79, H5.50, N16.48
34	$C_{26}H_{28}N_6O_5$	504.54	C61.89, H5.59, N16.65	C62.18, H5.86, N16.31
35	$C_{28}H_{29}N_5O_4$	499.56	C67.31, H5.85, N14.01	
	$C_{28}H_{29}N_5O_4 \cdot 0.27MeOH$	508.22	C66.81, H5.97, N13.78	C66.73, H5.87, N13.61
36	$C_{36}H_{41}N_5O_4$	607.75	608.3237 (M+H)	608.3251
37	$C_{36}H_{29}N_5O_4$	595.65	C72.59, H4.91, N11.75	
	$C_{36}H_{29}N_5O_4 \cdot 0.60H_2O$	606.47	C71.30, H5.02, N11.55	C71.48, H4.98, N11.45
38	$C_{35}H_{29}N_5O_5$	599.64	599.2169	599.2171

Example 56 Prevention of Myocardial Necrosis Following Ninety Minute LAD Occlusion by 8-[4-[((4-Cyano)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (27).

The compounds of the invention were tested for their ability to block A_{2B} receptors to show that mast cell degranulation can be reduced or prevented. In addition, this example shows that these antagonists could prevent or markedly attenuate the extent of myocardial infarction that occurred during coronary artery occlusion.

The left anterior descending (LAD) coronary artery of a group of dogs was isolated and encircled with a snare occluder. The dogs LAD artery blood supply was occluded for 90 minutes. The test solutions were administered intracoronary beginning immediately prior to the 90 minute occlusion interval and continued for two hours post-reperfusion (Figure 6). One group of three dogs were administered a solution containing the (4-cyano)phenyl compound, prepared in Example 18, infused at a concentretion of 200nM at a rate of 1.0 mL /min. by intracoronary (i.c.) infusion into the LAD. A second group of four dogs were administered a solution containing the vehicle (carrier). Regional myocardial blood flow was measured at baseline, during LAD occlusion and for 2 hrs after reperfusion using radiolabeled microspheres (mic).

The results are illustrated in Figures 7 and 8. These figures show that the infusion of the test compound during the 90 minute occlusion dramatically attenuated infarct size compared with dogs that were untreated.

Example 57 Specific binding of tritiated 8-[4-[((4-cyano)phenyl-carbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (27).

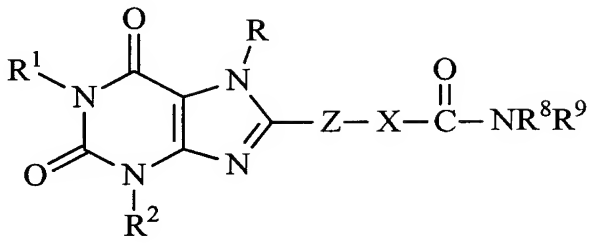
The compounds of the invention were tested for their specific binding at A_{2B} receptors. Compound **27**, 8-[4-[((4-cyano)phenylcarbamoylmethyl)-oxy]phenyl]-1,3-di-(n-propyl)xanthine was tritiated by New England Nuclear. The tritiated compound was used in radioligand binding assays on rat bladder membranes as described hereinabove substituting rat bladder cells for the cultured cells. The results show that specific binding (483 fmol/mg protein) with a K_D of 1.82 nM of the test compound in the tissue was detected.

The results are illustrated in Figure 9. This is a plot of the bound test compound vs. the unbound test compound. The graph shows both specific and nonspecific binding.

All patents, patent applications, books and literature cited in the specification are hereby incorporated by reference in their entirety. In the case of any inconsistencies, the present disclosure, including any definitions therein will prevail. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

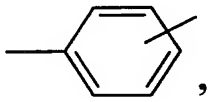
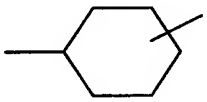
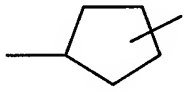
WHAT IS CLAIMED IS:

1. A compound of formula I:



I

wherein R, and R^1 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, heterocycle, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or heteroaryl;

Z is  ,  , or  ;

X is $(C_1$-$C_8)$alkylene, $(C_2$-$C_8)$alkenylene, $(C_2$-$C_8)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —$N(R^4)C(O)$—, —OC(O)—, —$N(R^5)(R^6)$—, —S—, —S(O)— or —SO_2—,

R^2 is hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$-alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —COOH and —SO_3H,

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl; and

wherein R^8 is hydrogen, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^9 is —$NR^{10}R^{11}$, or R^9 is $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2,

—CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H, and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, heteroaryl, —$C(O)(CH_2)_nCO_2R^{12}$, —$C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, —$C(O)R^{12}$, —$C(O)(C_3$-$C_8)$cycloalkyl or —$C(O)(C_3$-$C_8)$cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H;

wherein R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl;

wherein R^{21} and R^{22} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl;

provided that —NR^8R^9 is not aminoalkyl, aminodialkyl or hydrazino; and

provided that when R and R^8 are both H, and R^1 and R^2 are both alkyl, R^9 is not 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or

a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R and R^1 are independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$alkoxy, $(C_5$-$C_6)$cycloalkyl, $(C_6$-$C_{10})$cycloalkylalkyl, heterocycle, (C_6)aryl, $(C_7$-$C_{10})$aralkyl or heteroaryl;

X is $(C_1$-$C_6)$alkylene, $(C_2$-$C_6)$alkenylene, $(C_2$-$C_6)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —$N(R^4)$C(O)—, —OC(O)—, —$N(R^5)(R^6)$—, —S—, —S(O)— or —SO_2—;

R^2 is hydrogen, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$-alkoxy, $(C_5$-$C_6)$cycloalkyl, $(C_6$-$C_{10})$cycloalkylalkyl, (C_6)aryl, $(C_7$-$C_{10})$aralkyl or a heterocycle;

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_5$-$C_6)$cycloalkyl, (C_6)aryl, $(C_7$-$C_{10})$aralkyl or halo$(C_1$-$C_6)$alkyl groups; and

wherein R^8 is hydrogen, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_{10})$cycloalkylalkyl, $(C_7$-$C_{10})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, (C_6)aryl, $(C_7$-$C_{10})$aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is $(C_1$-$C_6)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_6)$alkenyl, (C_6)aryl, $(C_7$-$C_{10})$aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_6)$alkyl, halo$(C_1$-

C_6)alkyl, (C_2-C_6)alkenyl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15},—CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is —$NR^{10}R^{11}$, or R^9 is (C_3-C_6)cycloalkyl, (C_4-C_{10})cycloalkylalkyl, (C_7-C_{10})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is (C_1-C_6)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15},—CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_3-C_6)cycloalkyl, (C_6)aryl, (C_7-C_{10})aralkyl, heterocycle, heteroaryl, —$C(O)(CH_2)_nCO_2R^{12}$, —$C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, —$C(O)R^{12}$, —$C(O)(C_3$-$C_6)$cycloalkyl or —$C(O)(C_3$-$C_6)$cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, —OR^{15}, halo, —CN,

—NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H.

3. The compound according to claim 2, wherein R, R^1 and R^2 are independently hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_1-C_4)alkoxy, (C_5-C_6)cycloalkyl, (C_6-C_{10})cycloalkylalkyl, (C_6)aryl, or (C_7-C_{10})aralkyl;

Z is  ; and

X is O-(C_1-C_7)alkylene, O-(C_2-C_7)alkenylene, (C_1-C_8)alkylene or (C_2-C_8)alkenylene; wherein

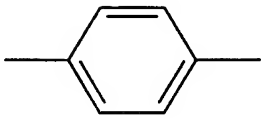
R^9 is (C_3-C_6)cycloalkyl, (C_4-C_{10})cycloalkylalkyl, (C_7-C_{10})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is (C_1-C_6)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15},—CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H.

4. The compound according to claim 2, wherein R, R^1 and R^2 are independently hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl,

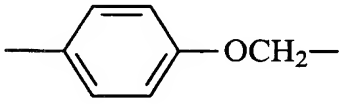
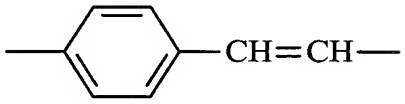
$(C_1$-$C_4)$alkoxy, $(C_5$-$C_6)$cycloalkyl, $(C_6$-$C_{10})$cycloalkylalkyl, (C_6)aryl, or $(C_7$-$C_{10})$aralkyl;

Z is  ;

X is O-$(C_1$-$C_7)$alkylene, O-$(C_2$-$C_7)$alkenylene, $(C_1$-$C_8)$alkylene or $(C_2$-$C_8)$alkenylene; and

R^9 is $—NR^{10}R^{11}$.

5. The compound according to claim 3, wherein —X—Z— is

 or 

R^1 and R^2 are independently $—CH_2CH_3$, $—CH_2CH=CH_2$, $—CH_2CH_2CH_3$ or cyclohexylmethyl.

6. The compound according to claim 5, wherein aryl is phenyl and aralkyl is benzyl.

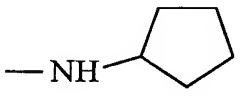
7. The compound according to claim 6, wherein R^9 is phenyl substituted with 1-3 substituents that are independently trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, benzyl, F, Cl, Br, I, —CN, $—NO_2$, $—CO_2R^{15}$, $—C(O)R^{16}$, $—NR^{13}R^{14}$ or $—C(O)NR^{17}R^{18}$, or benzyl, optionally substituted with 1-3 substituents that are independently alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, —OH, F, Cl, Br, I, —CN, $—NO_2$, $—CO_2R^{15}$, $—C(O)R^{16}$, $—NR^{13}R^{14}$ or $—C(O)NR^{17}R^{18}$.

8. The compound according to claim 7, wherein R^8 is hydrogen and R^9 is phenyl substituted with 1-3 substituents that are independently F, Cl, Br, I,

—CN, —COOH, —C(O)OCH_3, —C(O)CH_2CH_3, —C(O)CH_3, —C(O)NH_2 or —C(O)$NHCH_3$ or

benzyl, optionally substituted with 1-3 substituents that are independently —CH_2CH_3, F, Cl, Br, I, —CN, —COOH, —CO_2CH_3, —C(O)CH_2CH_3, —C(O)CH_3, —C(O)NH_2 or —C(O)$NHCH_3$.

9. The compound according to claim 5, wherein —NR^8R^9 is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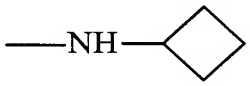
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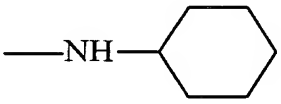
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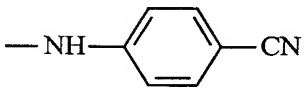
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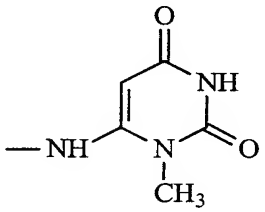
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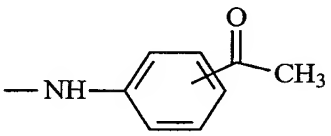
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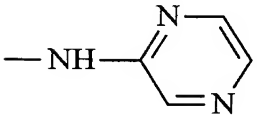
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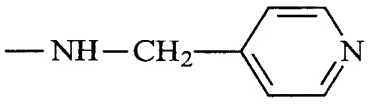
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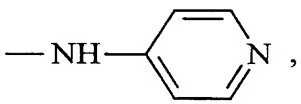
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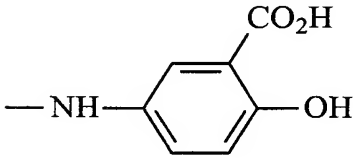
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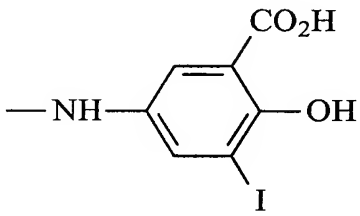
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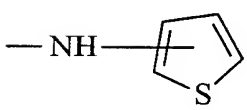
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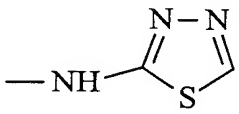
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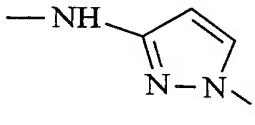
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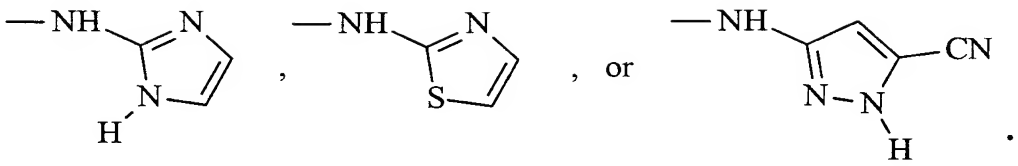
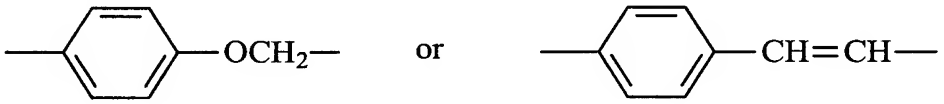


10. The compound according to claim 9, wherein R is H, R^1 and R^2 are each $—CH_2CH=CH_2$, and R^9 is 4-cyanophenyl.

11. The compound according to claim 9, wherein R is H, R^1 and R^2 are each $—CH_2CH_2CH_3$, and R^9 is 3-carboxy-4-hydroxyphenyl or 3-acetylphenyl.

12. The compound according to claim 4, wherein —X—Z— is

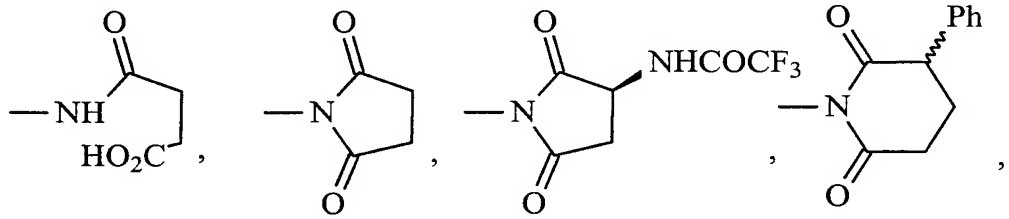


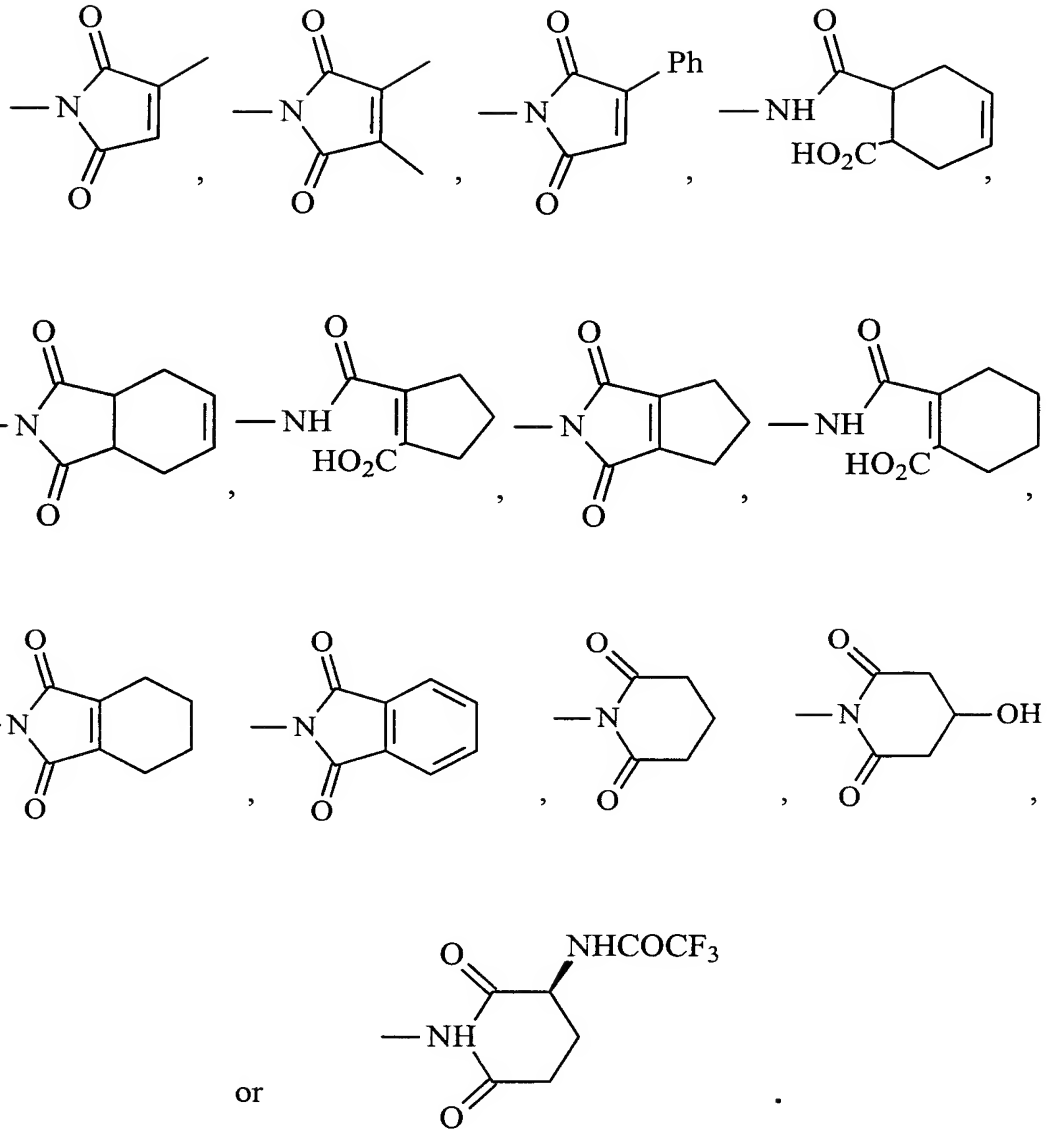
R^1 and R^2 are independently $—CH_2CH_3$, $—CH_2CH=CH_2$, $—CH_2CH_2CH_3$ or cyclohexylmethyl; and

R^8 is hydrogen, aryl or aralkyl.

13. The compound according to claim 12, wherein R^{10} and R^{11} are independently hydrogen, $—C(O)(CH_2)_nCO_2R^{12}$, $—C(O)CR^{21}=CR^{22}CO_2R^{12}$, $—C(O)R^{12}$, $—C(O)(C_3\text{-}C_6)$cycloalkyl, $—C(O)(C_3\text{-}C_6)$cycloalkenyl or wherein the R^{10} and R^{11} groups and the nitrogen atom taken together form said optionally substituted heterocycle or a heteroaryl ring, and n is 2.

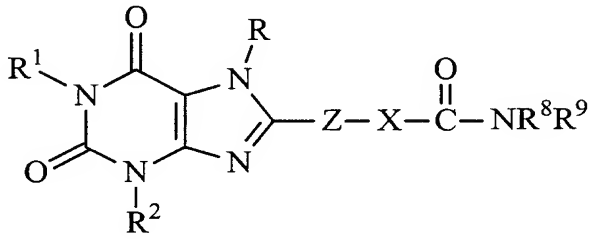
14. The compound of claim 13, wherein R^9 is





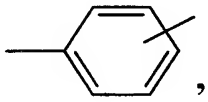
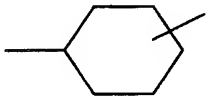
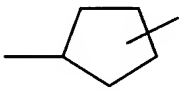
or

15. A compound of formula I:



I

wherein R and R^1 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, heterocycle, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or heteroaryl;

Z is  ,  , or  ;

X is $(C_1$-$C_8)$alkylene, $(C_2$-$C_8)$alkenylene, $(C_2$-$C_8)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —$N(R^4)C(O)$—, —$OC(O)$—, —$N(R^5)(R^6)$—, —S—, —S(O)— or —SO_2—,

R^2 is hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —COOH and —SO_3H,

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl; and

wherein R^8 is hydrogen, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^9 is $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H, and

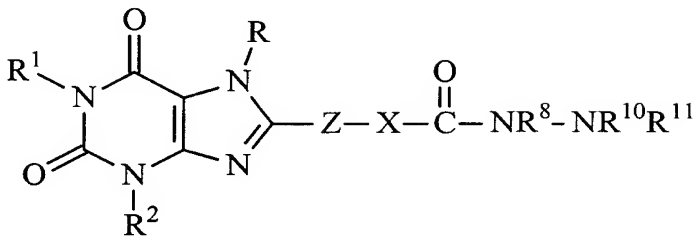
wherein, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl;

provided that —NR^8R^9 is not aminoalkyl or aminodialkyl; and

provided that when R and R^8 are both H, and R^1 and R^2 are both alkyl, R^9 is not 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or

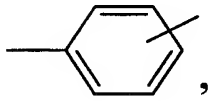
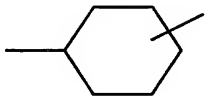
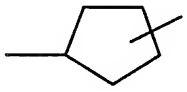
a pharmaceutically acceptable salt thereof.

16. A compound of formula II:



II

wherein R and R^1 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, heterocycle, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or heteroaryl;

Z is  ,  , or  ;

X is $(C_1$-$C_8)$alkylene, $(C_2$-$C_8)$alkenylene, $(C_2$-$C_8)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —$N(R^4)C(O)$—, —OC(O)—, —$N(R^5)(R^6)$—, —S—, —S(O)— or —SO_2—,

R^2 is hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —COOH and —SO_3H,

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl; and

wherein R^8 is hydrogen, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-

C_{18})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —$C(O)(CH_2)_nCO_2R^{12}$, —$C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, —$C(O)R^{12}$, —$C(O)$($C_3$-$C_8$)cycloalkyl or —$C(O)$($C_3$-$C_8$)cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H;

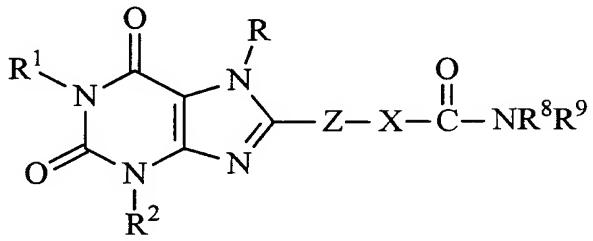
wherein R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18},R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl;

R^{21} and R^{22} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl;

provided that —NR^8—$NR^{10}R^{11}$ is not hydrazino; or

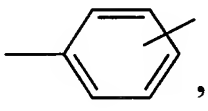
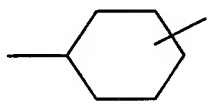
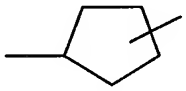
a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound of formula I:



I

wherein R, and R^1 are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, heterocycle, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or heteroaryl;

Z is  ,  , or  ;

X is (C_1-C_8)alkylene, (C_2-C_8)alkenylene, (C_2-C_8)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is

optionally replaced with a group having the formula —O—, —N(R^4)C(O)—, —OC(O)—, —N(R^5)(R^6)—, —S—, —S(O)— or —SO_2—,

R^2 is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)-alkoxy, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —COOH and —SO_3H,

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl; and

wherein R^8 is hydrogen, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —N$R^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)N$R^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —OC(O)R^{16}, —C(O)R^{16}, —N$R^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)N$R^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —N$R^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)N$R^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^9 is —N$R^{10}R^{11}$, or R^9 is (C_3-C_8)cycloalkyl, (C_4-C_{16})cyclo-alkylalkyl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15},

—$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H, and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, heteroaryl, —$C(O)(CH_2)_nCO_2R^{12}$, —$C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, —$C(O)R^{12}$, —$C(O)(C_3$-$C_8)$cycloalkyl or —$C(O)(C_3$-$C_8)$cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C_1-C_8)-

alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H;

wherein R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl;

wherein R^{21} and R^{22} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)-alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl;

provided that —NR^8R^9 is not aminoalkyl, aminodialkyl or hydrazino;and

provided that when R and R^8 are both H, and R^1 and R^2 are both alkyl, R^9 is not 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or

a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

18. The composition according to claim 17, wherein R and R^1 are independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_5-C_6)cycloalkyl, (C_6-C_{10})cycloalkylalkyl, heterocycle, (C_6)aryl, (C_7-C_{10})aralkyl or heteroaryl;

X is (C_1-C_6)alkylene, (C_2-C_6)alkenylene, (C_2-C_6)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —$N(R^4)C(O)$—, —OC(O)—, —$N(R^5)(R^6)$—, —S—, —S(O)— or —SO_2—;

R^2 is hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_1-C_4)-alkoxy, (C_5-C_6)cycloalkyl, (C_6-C_{10})cycloalkylalkyl, (C_6)aryl, (C_7-C_{10})aralkyl or a heterocycle;

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_5-C_6)cycloalkyl, (C_6)aryl, (C_7-C_{10})aralkyl or halo(C_1-C_6)alkyl groups; and

wherein R^8 is hydrogen, (C_3-C_6)cycloalkyl, (C_4-C_{10})cycloalkylalkyl, (C_7-C_{10})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-

C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is (C_1-C_6)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15},—CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is —$NR^{10}R^{11}$, or R^9 is (C_3-C_6)cycloalkyl, (C_4-C_{10})cycloalkylalkyl, (C_7-C_{10})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is (C_1-C_6)alkyl,substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_6)alkenyl, (C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is (C_6-C_{10})aryl,substituted with one or more substituents independently selected from the group consisting of (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15},—CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_3-C_6)cycloalkyl, (C_6)aryl, (C_7-C_{10})aralkyl, heterocycle,

heteroaryl, —C(O)$(CH_2)_nCO_2R^{12}$, —C(O)CR^{21}=$CR^{22}(CH_2)_mCO_2R^{12}$, —C(O)$R^{12}$, —C(O)$(C_3$-$C_6)$cycloalkyl or —C(O)$(C_3$-$C_6)$cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, (C_6)aryl, $(C_7$-$C_{10})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —$NR^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)$NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, (C_6)aryl, $(C_7$-$C_{10})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —$NR^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)$NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H.

19. The composition according to claim 18, wherein R, R^1 and R^2 are independently hydrogen, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$alkoxy, $(C_5$-$C_6)$cycloalkyl, $(C_6$-$C_{10})$cycloalkylalkyl, (C_6)aryl, or $(C_7$-$C_{10})$aralkyl;

Z is  ;

X is O-$(C_1$-$C_7)$alkylene, O-$(C_2$-$C_7)$alkenylene, $(C_1$-$C_8)$alkylene or $(C_2$-$C_8)$alkenylene; wherein

R^9 is $(C_3$-$C_6)$cycloalkyl, $(C_4$-$C_{10})$cycloalkylalkyl, $(C_7$-$C_{10})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, (C_6)aryl, $(C_7$-$C_{10})$aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —$NR^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)$NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is $(C_1$-$C_6)$alkyl,substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_6)$alkenyl,

(C_6)aryl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is (C_6-C_{10})aryl,substituted with one or more substituents independently selected from the group consisting of (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_7-C_{10})aralkyl, heteroaryl, halo, —OR^{15},—CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H.

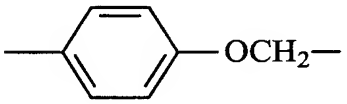
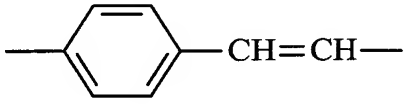
20. The composition according to claim 18, wherein R, R^1 and R^2 are independently hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_1-C_4)alkoxy, (C_5-C_6)cycloalkyl, (C_6-C_{10})cycloalkylalkyl, (C_6)aryl, or (C_7-C_{10})aralkyl;

Z is  ;

X is O-(C_1-C_7)alkylene, O-(C_2-C_7)alkenylene, (C_1-C_8)alkylene or (C_2-C_8)alkenylene; and

R^9 is —$NR^{10}R^{11}$.

21. The composition according to claim 19, wherein —Z—X— is

 or 

and R^1 and R^2 are independently —CH_2CH_3, —$CH_2CH{=}CH_2$, —$CH_2CH_2CH_3$ or cyclohexylmethyl.

22. The composition according to claim 21, wherein wherein aryl is phenyl and aralkyl is benzyl.

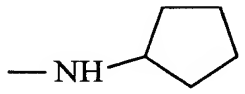
23. The composition according to claim 22, wherein R^9 is phenyl substituted with 1-3 substituents that are independently trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, alkenyl, benzyl, F, Cl, Br, I, —CN, —NO_2, —CO_2R^{15}, —$C(O)R^{16}$, —$NR^{13}R^{14}$ or —$C(O)NR^{17}R^{18}$,or

benzyl, optionally substituted with 1-3 substituents that are independently alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, alkenyl, —OH, F, Cl, Br, I, —CN, —NO_2, —CO_2R^{15}, —$C(O)R^{16}$, —$NR^{13}R^{14}$ or —$C(O)NR^{17}R^{18}$.

24. The composition according to claim 23, wherein R^8 is hydrogen and R^9 is phenyl substituted with 1-3 substituents that are independently F, Cl, Br, I, —CN, —COOH, —CO_2CH_3, —$C(O)CH_2CH_3$, —$C(O)CH_3$, —$C(O)NH_2$ or —$C(O)NHCH_3$ or

benzyl, optionally substituted with 1-3 substituents that are independently —CH_2CH_3, F, Cl, Br, I, —CN, —COOH, —CO_2CH_3, —$C(O)CH_2CH_3$, —$C(O)CH_3$, —$C(O)NH_2$ or —$C(O)NHCH_3$.

25. The composition according to claim 21, wherein —NR^8R^9 is: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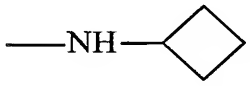
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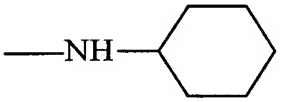
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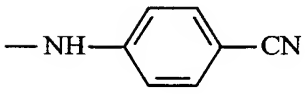
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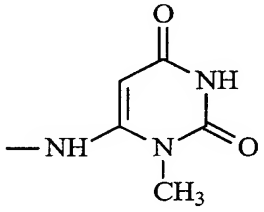
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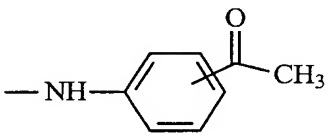
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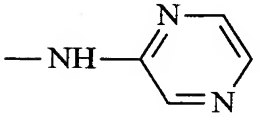
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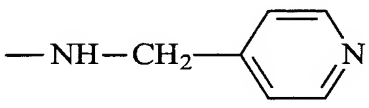
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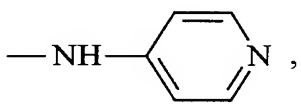
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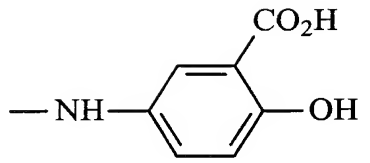
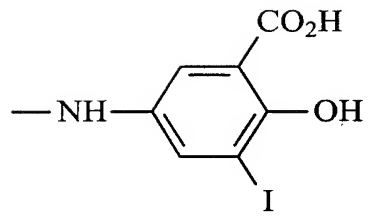
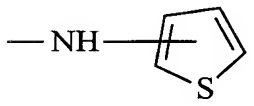
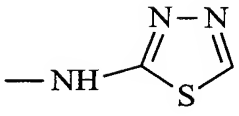
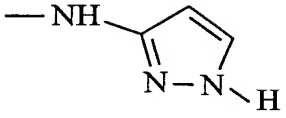
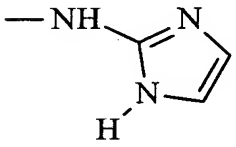
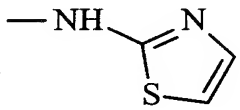
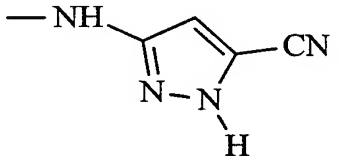
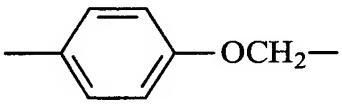
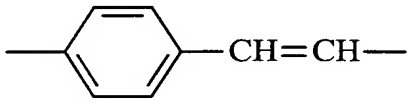









5 26. The composition according to claim 25, wherein R and R^8 are each H, R^1 and R^2 are each —$CH_2CH{=}CH_2$, and R^9 is 4-cyanophenyl.

27. The composition according to claim 26, wherein R and R^8 are each H, R^1 and R^2 are each —$CH_2CH_2CH_3$, and R^9 is 3-carboxy-4-hydroxyphenyl or 3-
10 acetylphenyl.

28. The composition according to claim 20, wherein —Z—X— is

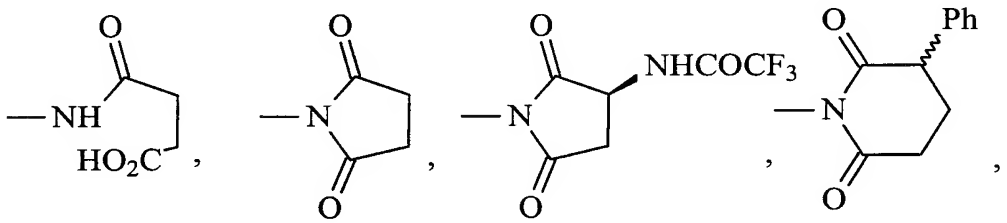

or


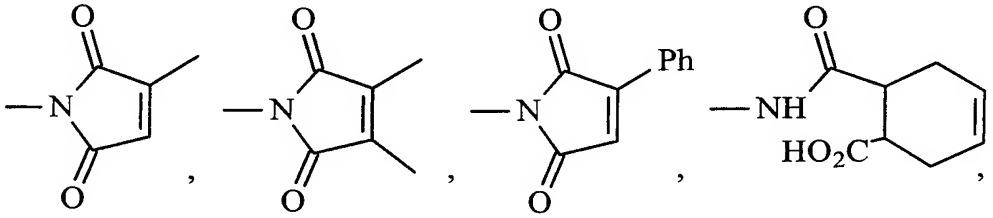
wherein R^1, and R^2 are independently —CH_2CH_3, —$CH_2CH{=}CH_2$,
15 —$CH_2CH_2CH_3$ or cyclohexylmethyl; and

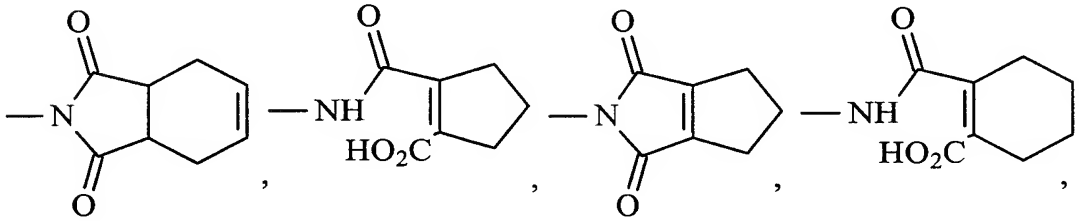
R^8 is hydrogen, aryl or aralkyl.

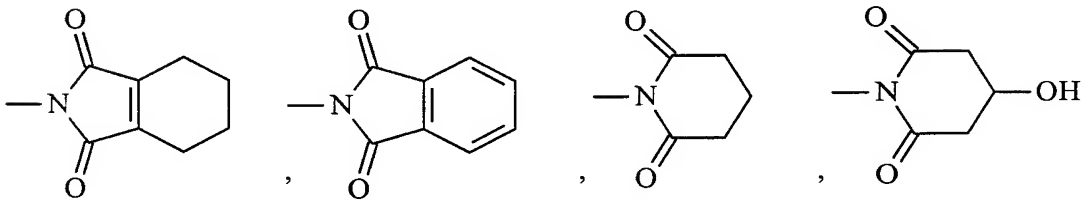
29. The composition according to claim 28, wherein R^{10} and R^{11} are independently hydrogen, —$C(O)(CH_2)_nCO_2R^{12}$, —$C(O)CR^{21}=CR^{22}CO_2R^{12}$, —$C(O)R^{12}$, —$C(O)(C_3$-$C_6)$cycloalkyl, —$C(O)(C_3$-$C_6)$cycloalkenyl or wherein the R^{10} and R^{11} groups and the nitrogen atom taken together form said optionally substituted heterocycle or a heteroaryl ring, and n is 2.

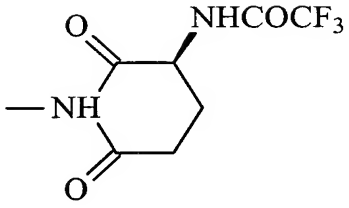
30. The composition of claim 29, wherein R^9 is



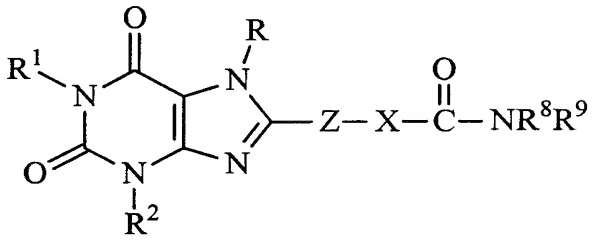






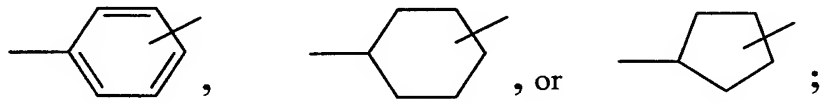
or  .

31. A pharmaceutical composition comprising a compound of formula I:



I

wherein R and R^1 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, heterocycle, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or heteroaryl;

Z is 

X is $(C_1$-$C_8)$alkylene, $(C_2$-$C_8)$alkenylene, $(C_2$-$C_8)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —$N(R^4)C(O)$—, —OC(O)—, —$N(R^5)(R^6)$—, —S—, —S(O)— or —SO_2—,

R^2 is hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$-alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —COOH and —SO_3H,

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl; and

wherein R^8 is hydrogen, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^9 is $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is $(C_1$-$C_8)$alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is $(C_6$-$C_{10})$aryl, substituted with one or more substituents independently selected from the group consisting of $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H, and

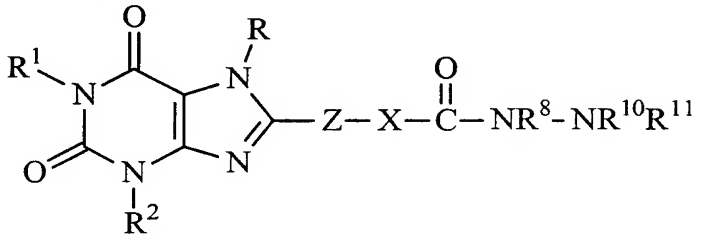
wherein, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl;

provided that —NR^8R^9 is not aminoalkyl or aminodialkyl; and

provided that when R and R^8 are both H, and R^1 and R^2 are both alkyl, R^9 is not 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or

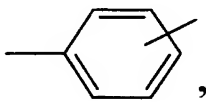
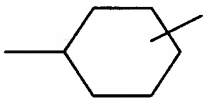
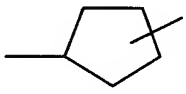
a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

32. A pharmaceutical composition comprising a compound of formula II:



II

wherein R and R^1 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, heterocycle, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or heteroaryl;

Z is  ,  , or  ;

X is $(C_1$-$C_8)$alkylene, $(C_2$-$C_8)$alkenylene, $(C_2$-$C_8)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is

optionally replaced with a group having the formula —O—, —N(R^4)C(O)—, —OC(O)—, —N(R^5)(R^6)—, —S—, —S(O)— or —SO_2—,

R^2 is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —COOH and —SO_3H,

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl;

wherein R^8 is hydrogen, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —NR^{13}R^{14}, —N(R^{23})C(O)R^{24}, —C(O)NR^{17}R^{18}, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —C(O)(CH_2)$_n$$CO_2$R^{12}, —C(O)CR^{21}=CR^{22}(CH_2)$_m$$CO_2$R^{12}, —C(O)R^{12}, —C(O)(C_3-C_8)cycloalkyl or —C(O)(C_3-C_8)cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl,

$(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H;

wherein R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18},R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl;

R^{21} and R^{22} are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl;

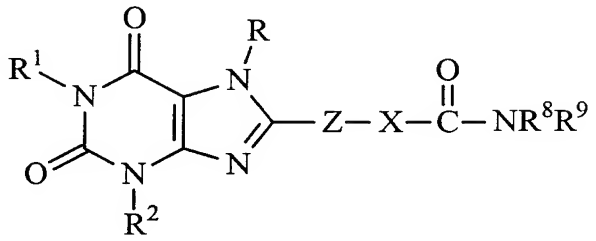
provided that —NR^8—$NR^{10}R^{11}$ is not hydrazino; or

a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

33. A method for treating asthma comprising administering an effective amount of a compound of claim 1, 15 or 16 to a mammal in need of such treatment.

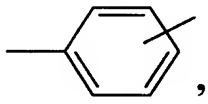
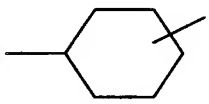
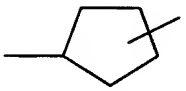
34. A method for treating diarrheal diseases, insulin resistance, diabetes, cancer, ischemia/reprefusion injuries, diabetic retinopathy or hyperbaric

oxygen-induced retinopathy, comprising administering an effective amount of a compound of formula I:



I

wherein R, and R^1 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, heterocycle, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or heteroaryl;

Z is  ,  , or  ;

X is $(C_1$-$C_8)$alkylene, $(C_2$-$C_8)$alkenylene, $(C_2$-$C_8)$alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R^4)C(O)—, —OC(O)—, —N(R^5)(R^6)—, —S—, —S(O)— or —SO_2—,

R^2 is hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$-alkoxy, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH_2, —NHR^7, —CN, —COOH and —SO_3H,

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl or halo$(C_1$-$C_6)$alkyl; and

wherein R^8 is hydrogen, $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_{16})$cycloalkylalkyl, $(C_7$-$C_{18})$aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_7$-$C_{18})$aralkyl,

heteroaryl, halo, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^8 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^8 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; and

wherein R^9 is —$NR^{10}R^{11}$, or R^9 is (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_7-C_{18})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or

R^9 is (C_1-C_8)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H; or

R^9 is (C_6-C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, —CN, —NO_2, —CO_2R^{15}, —$OC(O)R^{16}$, —$C(O)R^{16}$, —$NR^{13}R^{14}$, —$N(R^{23})C(O)R^{24}$, —$C(O)NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} and —SO_3H, and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, heteroaryl, —$C(O)(CH_2)_nCO_2R^{12}$, —$C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$,

—C(O)R^{12}, —C(O)(C_3-C_8)cycloalkyl or —C(O)(C_3-C_8)cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —$NR^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)$NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —$NR^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)$NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H; wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_{16})cycloalkylalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C_1-C_8)alkyl, halo(C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl, heteroaryl, —OR^{15}, halo, —CN, —NO_2, —CO_2R^{15}, —OC(O)R^{16}, —C(O)R^{16}, —$NR^{13}R^{14}$, —N(R^{23})C(O)R^{24}, —C(O)$NR^{17}R^{18}$, —SR^{19}, —SO_2R^{20} or —SO_3H;

wherein R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{23} and R^{24} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl or halo(C_1-C_6)alkyl;

wherein R^{21} and R^{22} are independently hydrogen, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl, (C_7-C_{18})aralkyl;

or a pharmaceutically acceptable salt thereof to a mammal in need of such treatment.

35. A therapeutic method for preventing or treating a pathological condition or symptom in a mammal, wherein the activity of adenosine A_{2B} receptors is implicated and antagonism of its action is desired comprising

administering to the mammal an effective amount of a compound of claim 1, 15 or 16.

36. The compound of claim 1, wherein one of the atoms of said compound is replaced by its radionuclide.

37. The compound of claim 36, wherein the radionuclide is tritium, or radioactive iodine.

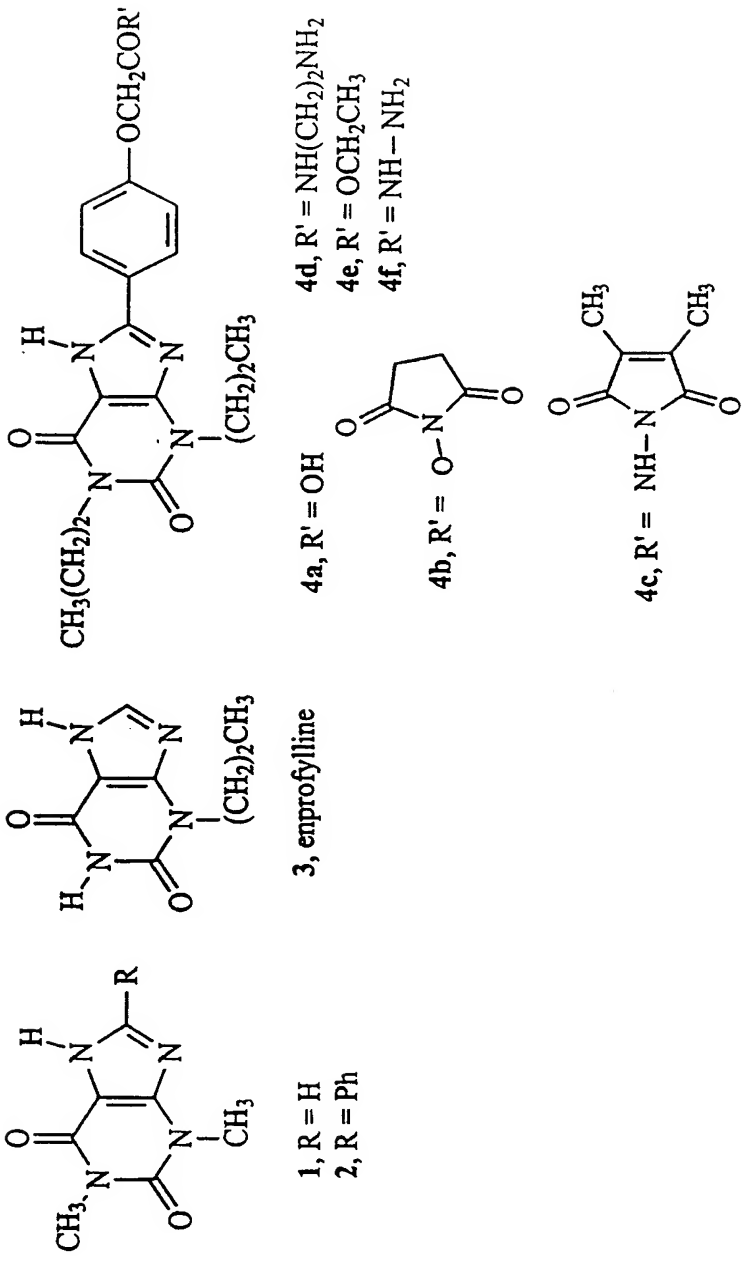

1, R = H
2, R = Ph
3, enprofylline
4a, R' = OH
4b, R' = O–N
4c, R' = NH–N
4d, R' = NH(CH2)2NH2
4e, R' = OCH2CH3
4f, R' = NH–NH2

FIG. 1

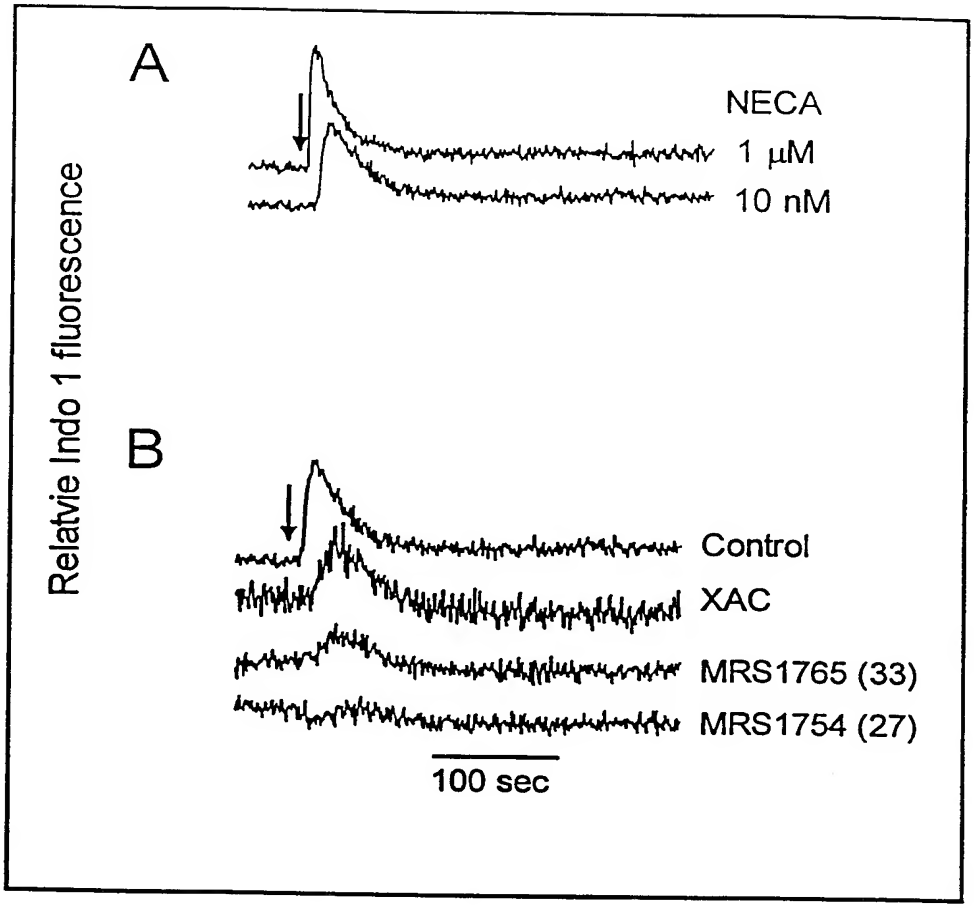
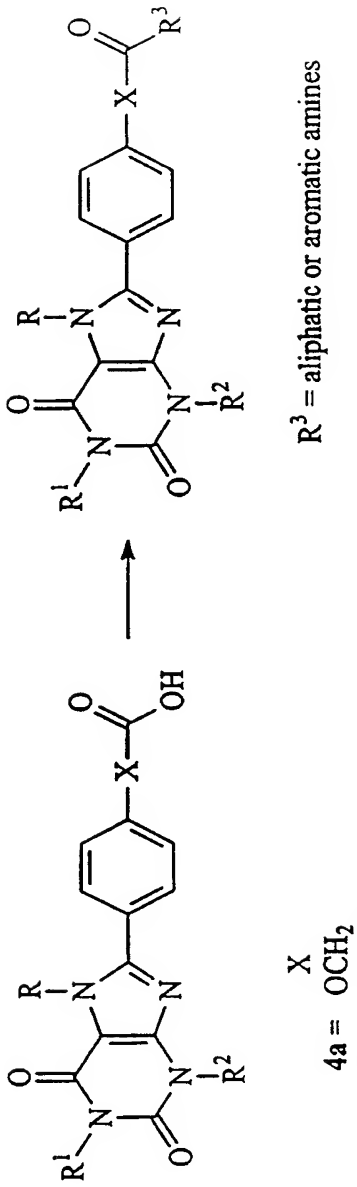

A
NECA
1 μM
10 nM
Relative Indo 1 fluorescence
B
Control
XAC
MRS1765 (33)
MRS1754 (27)
100 sec

FIG. 2



X
4a = OCH_2
4g = CH=CH

R^3 = aliphatic or aromatic amines

Reagents: 1) EDAC, DMAP, amines in DMF/CH_2Cl_2; 2) BOP-Cl, triethylamine, amines in CH_2CL_2; or 3) $SOCl_2$; amines in pyridine/CH_2Cl_2.

FIG. 3

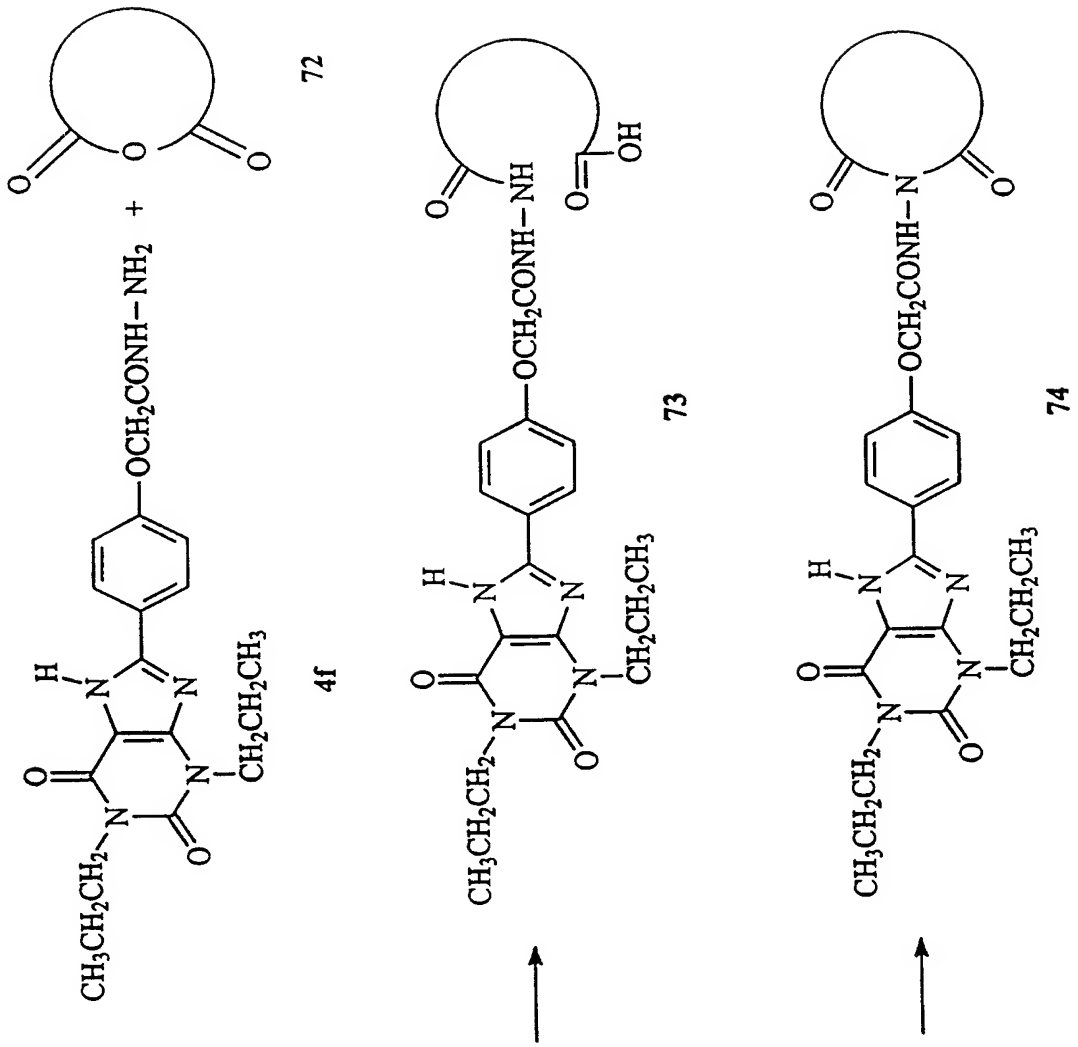


FIG. 4

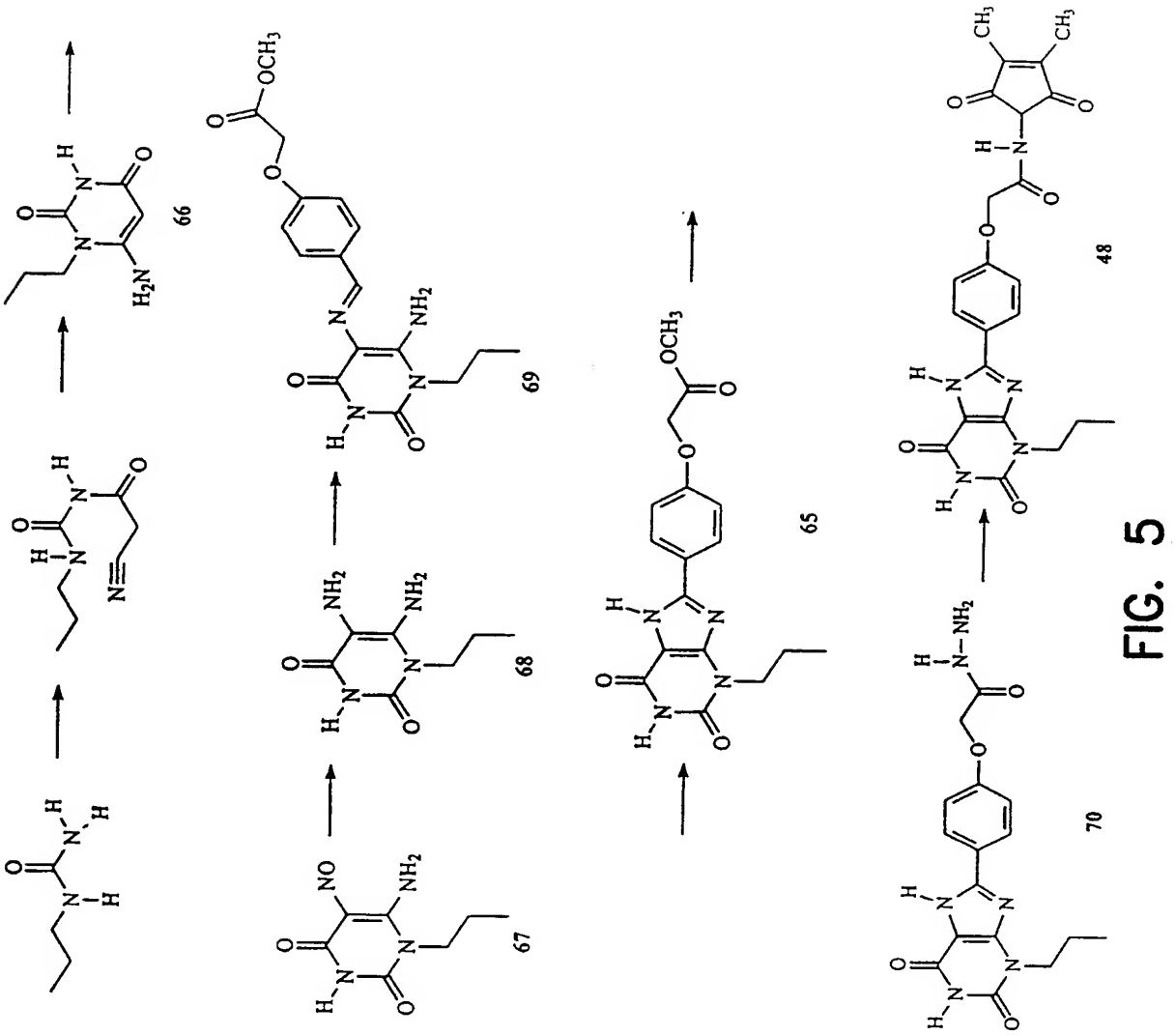
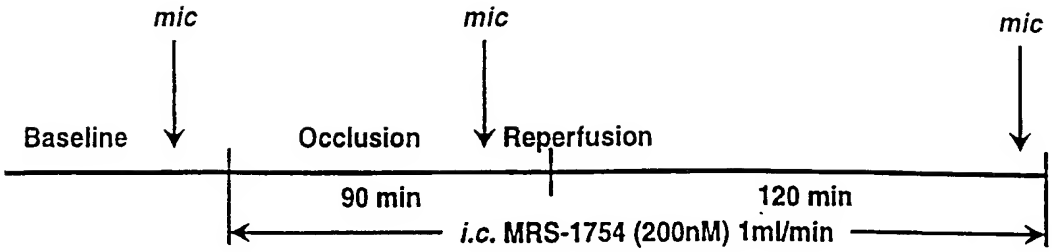


FIG. 5



Blood Sampling from CS

Baseline (x 2), 30 sec, 60 sec, 90 sec, 2 min, 3 min, 5 min, 10 min, 15 min, 30 min

FIG. 6

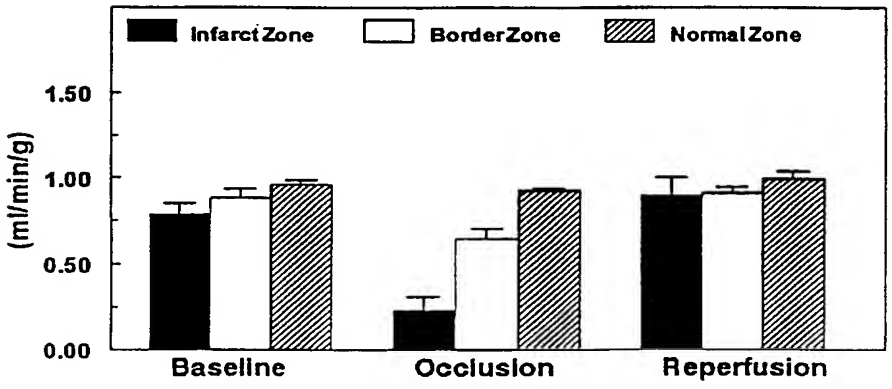


FIG. 7

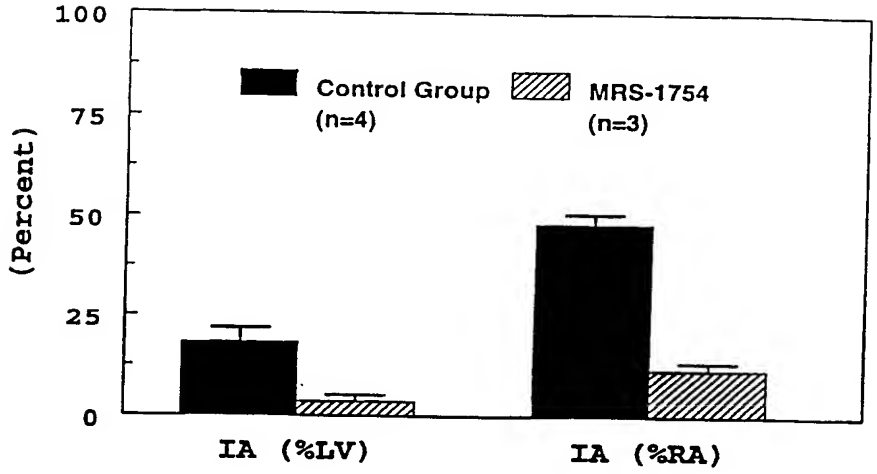
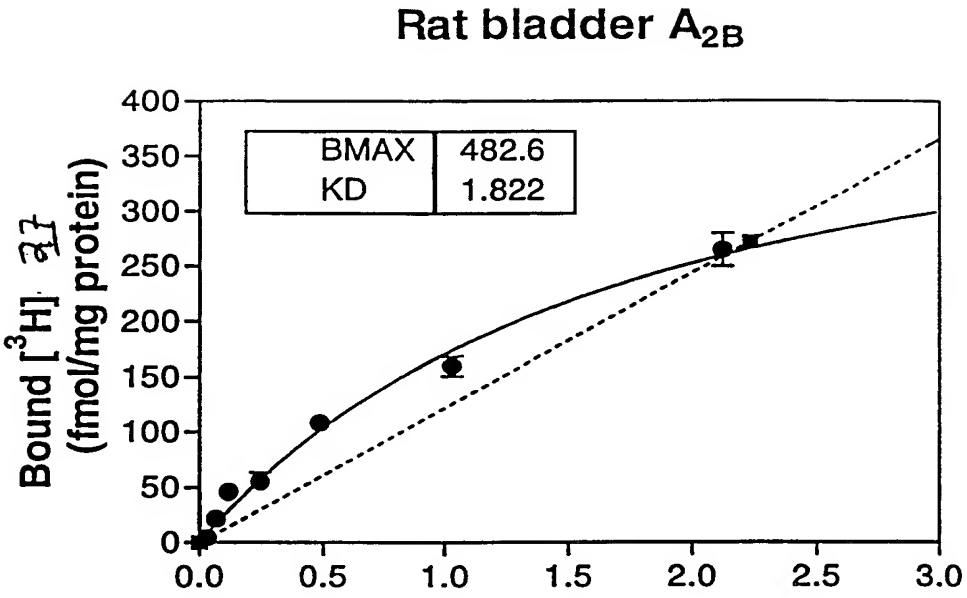


FIG. 8



[^{3}H] 8-[4-[((4-Cyano)phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (27).

------ Specific binding (•).
------- Nonspecific binding.

FIG. 9